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219

15

ARCHIVES OF Neurology

JANUARY 1991

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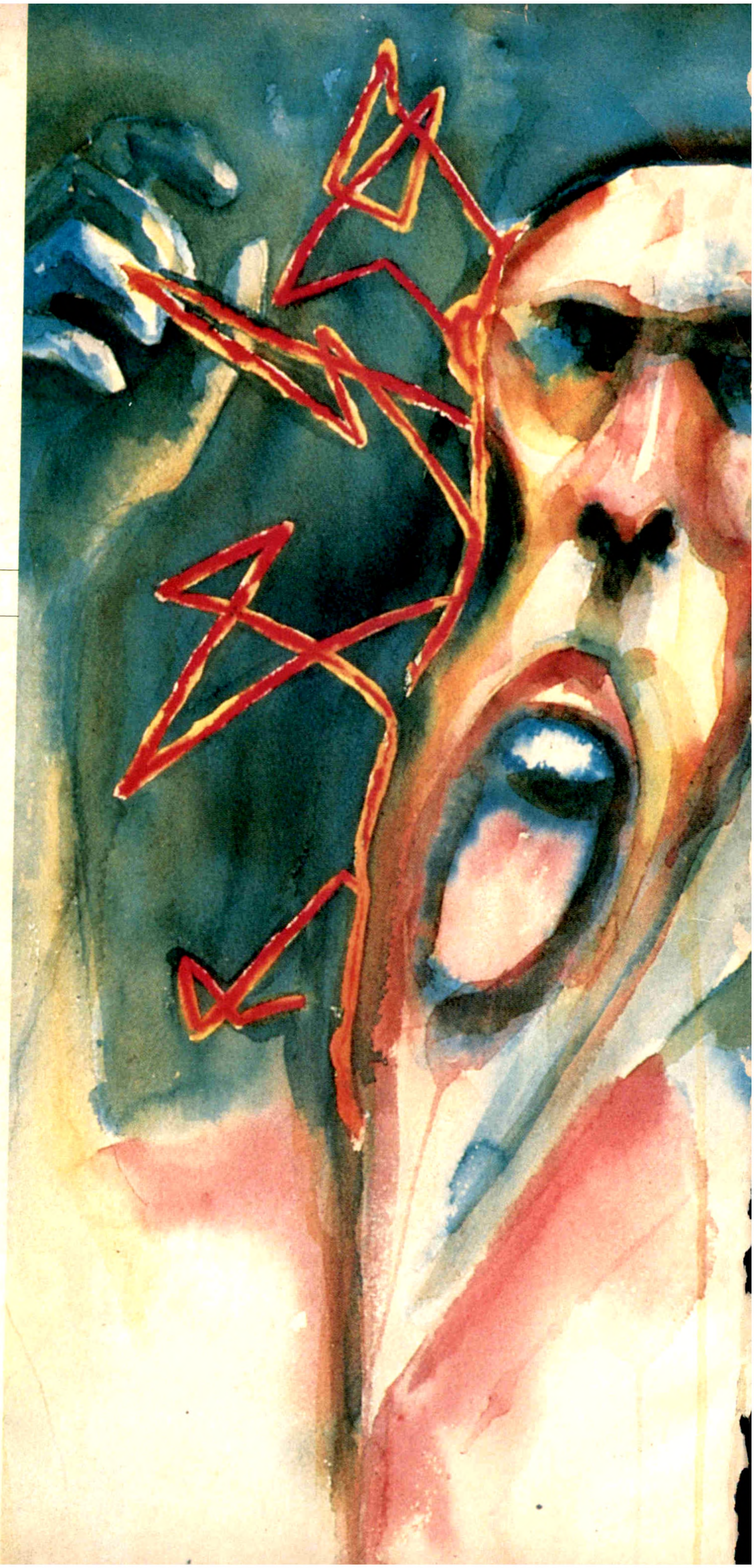
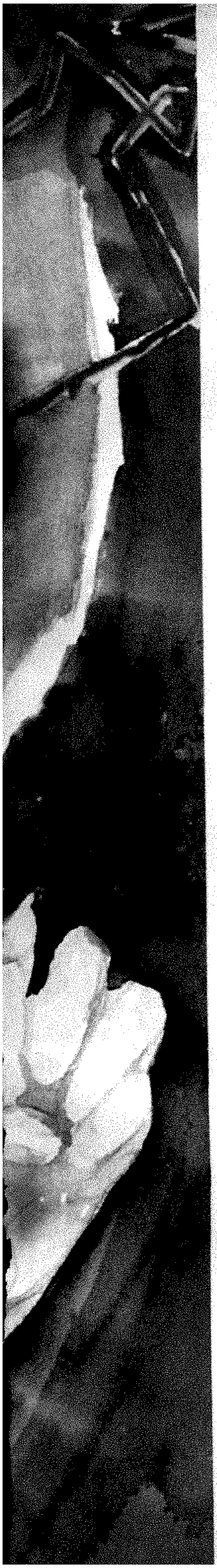
Volume 48, Number 1

American Medical Association
Physicians dedicated to the health of America

HEADACHE DESCRIBED



"Headache"—a personal interpretation of headache pain by John Crowley, a headache patient.



P24,923

HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL WITH CODEINE III CAPSULES

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

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Corporation, E. Hanover, NJ 07936 (201) 503-7500

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming]; butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset, lightheadedness and heavy eyelids, and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse ev reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiori with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patie

The prescriber should be aware that these figures cannot be used to predict the incidence of side effec the course of usual medical practice where patient characteristics and other factors differ from those that preva in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clin investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

Body System/ Adverse Event	Incidence Rate of Adverse Events Fiorinal®/Codeine (N = 382)	Placebo (N = 37
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proporti of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reporte on at least one occasion, an adverse event of the type cited. All reported adverse events, except those alrea presented in the previous table, are included. It is important to emphasize that, although the adverse events report did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caus by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event wh occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequ is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adve events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spe numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been rece since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, li decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unc sciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointesti spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromy (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorin with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, pe ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolon periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administra and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potentia being abused. Psychological dependence, physical dependence, and tolerance may develop upon repe administration and it should be prescribed and administered with the same degree of caution appropriate to use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical depend may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barb addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the s level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbitu is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually dec over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gr withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withd regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decrea the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable m to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overd is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyper acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthe hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restless tremor, and delirium, tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pin pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® Codeine. However, because strategies for the management of an overdose continually evolve, consultation regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with e in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are prese if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkaliza the urine, and correction of electrolyte disturbances should be accomplished through administration of intrav fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypote may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infus severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifes Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid ove Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should b under continued surveillance and repeated doses of the antagonist should be administered as needed to m adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant resp or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

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CALENDAR 13

LETTERS TO THE EDITOR

Migraine With Vasospasm and Delayed Intracerebral Hemorrhage 17
Yves De Smet, MD, Jean Marie Brucher, MD, Brussels, Belgium

Migraine and Intracerebral Hemorrhage 17
J. Vázquez-Cruz, MD, J. Alvarez-Sabin, MD, Barcelona, Spain

In Reply 17
Andrew J. Cole, MD, Baltimore, Md;
Michael Aubé, MD, Montreal, Quebec

Isopropyl Alcohol Intoxication 18
Keith Wrenn, MD, Rochester, NY

In Reply 18
Louis R. Caplan, MD; Nathaniel Katz, MD; Richard Scheife, DPharm;
Jaime Rich, MD, Boston, Mass

Seizures After Stroke 18
C. Z. Zhu, MD, J. W. Norris, MD, Toronto, Ontario

In Reply 19
Christine J. Kilpatrick, MD, FRACP; Stephen M. Davis, MD, FRACP;
Brian M. Tress, MD, FRCR, FRACR; Stephen C. Rossiter, BApplSc;
John L. Hopper, MSc, PhD;
Michelle L. Vandendriesen, MBBS, Parkville, Victoria, Australia

Is Radiosurgery All That It Appears to Be? 19
Bennett M. Stein, MD; J. P. Mohr, MD;
M. B. Sisti, MD, New York, NY

In Reply 20
L. Dade Lunsford, MD; John C. Flickinger, MD;
Robert J. Coffey, MD, Pittsburgh, Pa

American Society of Neuroimaging
14th Annual Meeting
February 5-10, 1991
Hilton at Walt Disney World Village
Orlando, Florida

The American Society of Neuroimaging is pleased to announce tha their 14th Annual Meeting will be held February 5-10, 1991, at the Hilton at Walt Disney World Village, Orlando, Florida.

The major emphasis of the meeting will be on the latest advance in the science of neuroimaging. The Education Program is designed for the clinical practice of neurology and for residents. This includes both basic and advanced programs with certification examinations. A special hands-on Transcranial Doppler Workshop will be featured. Due to heavy demand, early registration for eduational courses is requested. Make plans n to attend.

MEETING SCHEDULE

uesday, February 5, 1991

loming	
8:00-12:00	Basic Ultrasound
8:00-12:00	Applied MRI Physics for Technologists, Basic Scientists and Physicians
fternoon	
2:00- 6:00	Basic Ultrasound
2:00- 6:00	Applied MRI Physics for Technologists, Basic Scientists and Physicians
vening	
5:00- 7:30	Cocktail Reception
7:00-10:00	Hands-On Workshop: Neurosonology

ednesday, February 6, 1991

orning	
3:30- 8:00	Technical Exhibits and Scientific Posters
:45- 8:45	Breakfast Seminar: Laboratory Management/Chair: J. Toole
:00-12:30	Advanced Ultrasound
temoon	
:00- 6:00	Clinical MRI: Brain/Co-Chairs: I. Polachini, A. Carr
ening	
:00- 8:00	Exhibits & Poster Stand-by/Wine and Cheese Reception

Thursday, February 7, 1991

Morning	
8:30- 5:30	Technical Exhibits and Scientific Po
6:45- 8:45	Breakfast Seminar: Case Studies in Neuroimaging/Chair: I. Polachini
9:00-12:30	Clinical MRI: Brain
Afternoon	
2:00- 6:00	Clinical MRI: Spine
Evening	
6:00-11:00	Banquet: Cook-Out

Friday, February 8, 1991

Morning	
6:45- 8:45	Breakfast Seminar: SPECT & PET/ Masdeu
9:00-11:00	Advanced Ultrasound
11:00-12:30	Awards and Business Meeting
Afternoon	
2:00- 6:00	Advanced Topics in Magnetic Reson

Saturday, February 9, 1991

Morning	
6:45- 7:45	Breakfast Seminar: Magnetic Encepholography/Chair: W. McKin
8:00- 1:00	Interventional Neuroimaging/Chairs: Prockop, R. Smith
Afternoon	
2:00- 6:00	Certification Examinations

Sunday, February 10, 1991

Athletic Events

ASN and AAN members will automatically receive registration materials. Nonmembers interested in attending the Annual Meetin or receiving membership information should contact:

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ARCHIVES

EDITORIALS

The Pathogenesis of Dermatomyositis 21
Robert C. Griggs, MD, Rochester, NY;
George Karpati, MD, Montreal, Québec

Caring for the Uninsured and Underinsured 23
Matthew Menken, MD, Somerset, NJ

1990 Reviewers 24
Robert J. Joynt, Rochester, NY

ORIGINAL CONTRIBUTIONS

The Relationship of Complement-Mediated Microvasculopathy to the Histologic Features and Clinical Duration of Disease in Dermatomyositis 26
John T. Kissel, MD; Richard K. Halterman; Kottil W. Rammohan, MD;
Jerry R. Mendall, MD, Columbus, Ohio

Early Combination of Selegiline and Low-Dose Levodopa as Initial Symptomatic Therapy in Parkinson's Disease: Experience in 26 Patients Receiving Combined Therapy for 26 Months 31
T. S. Elizan, MD; D. A. Moros, MD; M. D. Yahr, MD, New York, NY

Ideomotor Apraxia in Huntington's Disease 35
Paul A. Shelton, MD, Winnipeg, Manitoba;
David S. Knopman, MD, Minneapolis, Minn

Initial Therapy of Patients With Wilson's Disease With Tetrathiomolybdate 42
George J. Brewer, MD; Robert D. Dick; Vilma Yuzbasiyan-Gurkin, PhD;
Roberta Tankanow, MS; Anne B. Young, MD;
Karen J. Kluin, MS, Ann Arbor, Mich

The Neural Substrate of Memory Impairment Demonstrated by the Intracarotid Amobarbital Procedure 48
Kimberlee J. Sass, PhD; Todd Lencz; Michael Westerveld, PhD;
Robert A. Novelly, PhD; Dennis D. Spencer, MD;
Jung H. Kim, MD, New Haven, Conn

Dominant-Side Intracarotid Amobarbital Spares Comprehension of Word Meaning 55
John Hart, Jr, MD; Ronald P. Lesser, MD; Robert S. Fisher, MD, PhD;
Pamela Schwerdt; R. Nicholas Bryan, MD, PhD;
Barry Gordon, MD, PhD, Baltimore, Md

Memory Complaints in Older Adults: Fact or Fiction? 61
Karen I. Bolla, PhD; Karen N. Lindgren; Cathy Bonaccorsy;
Margit L. Bleecher, MD, PhD, Baltimore, Md

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presents the
Third Annual Symposium on

Treatment of Headaches and Facial Pain

Sunday, May 5, 1991
at the Halloran House, New York, NY

Downstate Headache Center Faculty:	Guest Faculty:
Ronald Burakoff, DDS	Joel Saper, MD
Baruch Fishman, PhD	Glen Solomon, MD
Richard Lechtenberg, MD	Seymour Solomon, MD
Alexander Mauskop, MD	

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A one-day Basic Electromyography course will be held on June 23. Exhibit and poster dates are set for June 21 and 22 with poster presentation date on June 21.

For membership information, meeting details or abstract forms write:

Marlene Richard Fairbanks; Massachusetts General Hospital;
Clinical Neurophysiology Lab; Boston, Massachusetts 02114 or
Fax request for information to 617-726-2019. Tele. 617-726-8736.

NEW I

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ARCHIVES

Antibodies to Myelin-Associated Glycoprotein Are Found in Cerebrospinal Fluid in Polyneuropathy Associated With Monoclonal Serum IgM 66
Mabel Cruz, MD; Yu-Ping Jiang, MD, Stockholm, Sweden;
Jan Ernerudh, MD, PhD, Linköping, Sweden; Göran Solders, MD, PhD,
Tomas Olsson, MD, PhD, Stockholm, Sweden;
Per-Olov Osterman, MD, PhD, Uppsala, Sweden;
Hans Link, MD, PhD, Stockholm, Sweden

On Drawing Impairment in Alzheimer's Disease 73
Andrew Kirk, MD, Andrew Kertesz, MD, London, Ontario

A Trial of Thiamine in Alzheimer's Disease 81
K. A. Nolan, PhD; R. S. Black, MD; K. F. R. Sheu, PhD;
J. Langberg; J. P. Blass, MD, PhD, White Plains, NY

Nystagmus of Pelizaeus-Merzbacher Disease: A Magnetic Search-Coil Study 87
Jonathan D. Trobe, MD, Ann Arbor, Mich;
James A. Sharpe, MD, Toronto, Ontario;
David K. Hirsh, MD; Stephen S. Gebarski, MD, Ann Arbor, Mich

HISTORY OF NEUROLOGY

James Parkinson: On Child Abuse and Other Things 95
Robert D. Currier, MD, Mary M. Currier, MD, MPH, Jackson, Miss

OBSERVATIONS

Anton's Syndrome in a Patient With Posttraumatic Optic Neuropathy and Bifrontal Contusions 101
Keith D. McDaniel, MD, Leslie D. McDaniel, MD, Rochester, NY

Pupil-Sparing Oculomotor Nerve Palsy Due to Midbrain Infarction 105
Lenore A. Breen, MD, Morgantown, WVa;
Hanns C. Hopf, MD, Mainz, Federal Republic of Germany;
Bradley K. Farris, MD, Oklahoma City, Okla;
Ludwig Gutmann, MD, Morgantown, WVa

Congenital Monomelic Hypertrophy With Progressive Myopathy 107
Amitabh Shukla, MD, Burlington, Vt; Colin D. Hall, MD, Chapel Hill, NC;
Walter G. Bradley, DM, FRCP, William W. Pendlebury, MD, Burlington, Vt

REGULAR DEPARTMENTS

Instructions for Authors 14

Index to Advertisers 16

Classified Advertising 112

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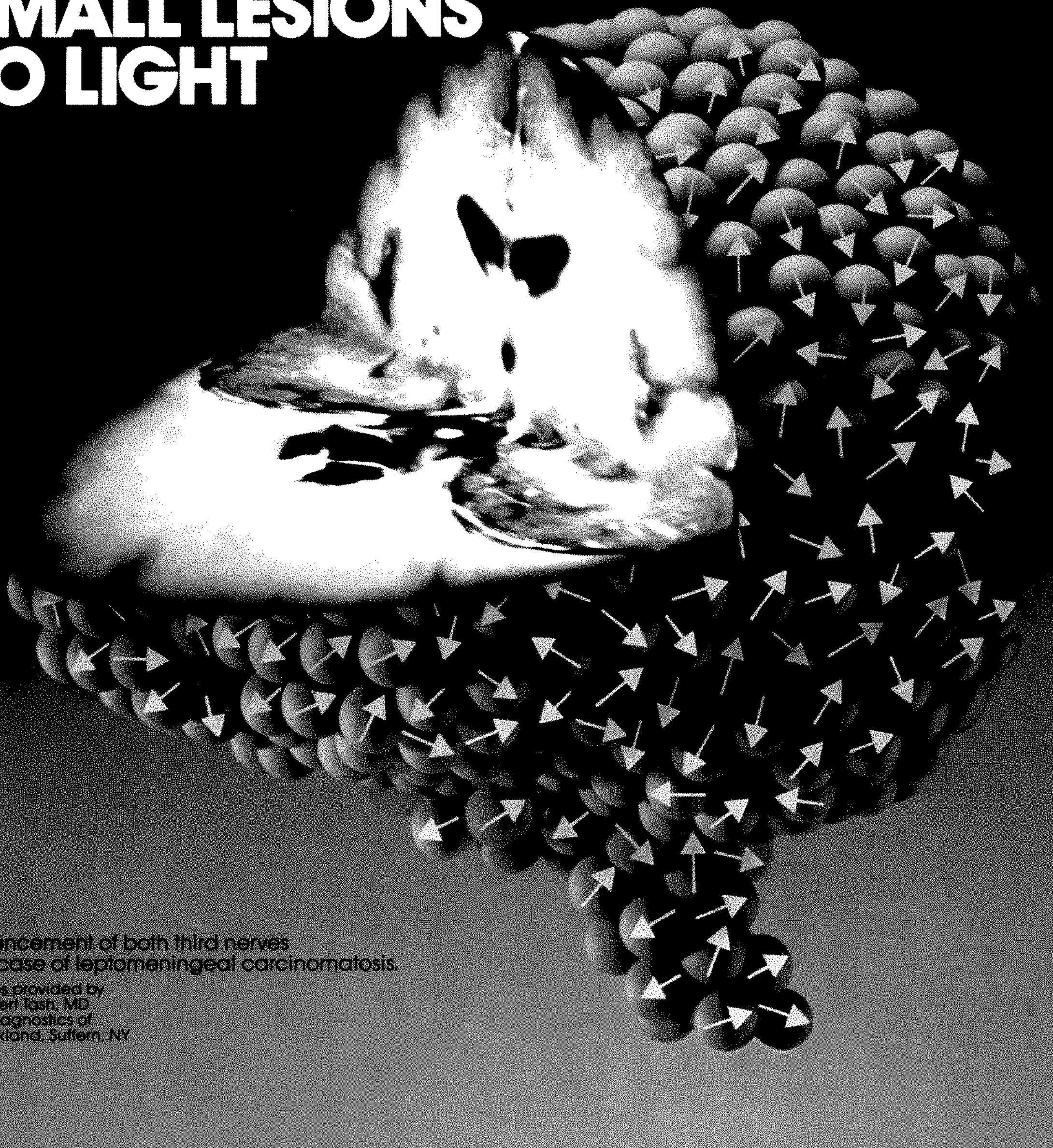
IN BRAIN METASTASES

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

BRINGS
SMALL LESIONS
TO LIGHT



Enhancement of both third nerves
in a case of leptomeningeal carcinomatosis.

Figures provided by
Robert Tash, MD
MRI Diagnostics of
Rockland, Suffern, NY

BERLEX
IMAGING

Please see brief summary of
prescribing information on last pag
of this advertisement.

A CASE FOR *Magnevist*®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

THE CASE: Four years after a radical mastectomy and chemotherapy treatment for breast carcinoma, a 63-year-old female presented with deep vein thrombosis. Metastatic spread to the brain had to be ruled out before anticoagulation therapy could be initiated.

CT DID NOT SHOW IT CLEARLY ENOUGH

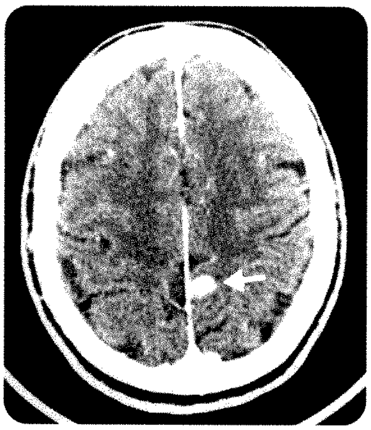


Figure 1. Contrast CT scan shows a circumscribed lesion in left parasagittal region (arrow), consistent with either metastasis or meningioma.

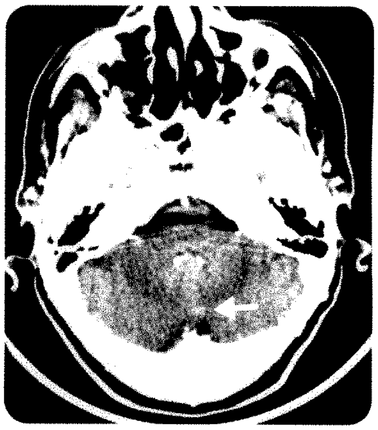


Figure 2. Contrast CT scan through posterior fossa suggests punctate area of contrast uptake in the vermis (arrow).

MRI ALONE WAS NOT DIAGNOSTIC

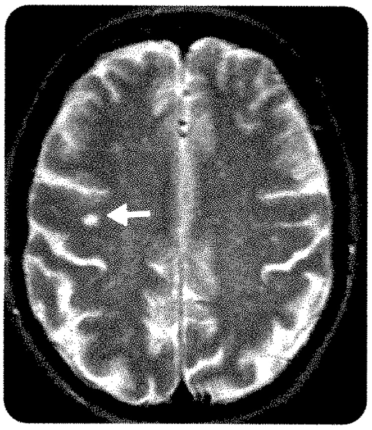


Figure 3. T2-weighted (TR 2000/TE 80) image shows area of high signal intensity in right frontoparietal region (arrow). Differential considerations include metastasis, small infarct, and demyelination. The lesion in left parasagittal region, seen in Figure 1, is not visualized.

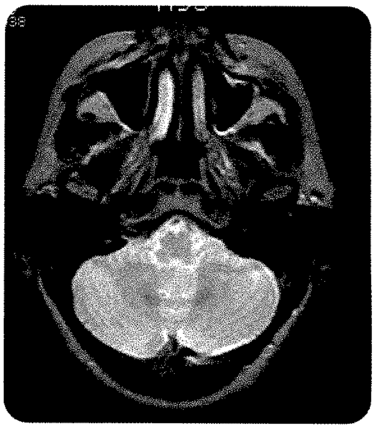


Figure 4. T2-weighted (TR 2000/TE 80) image through posterior fossa shows no abnormalities.

MAGNEVIST® INJECTION: A CRITICAL STEP IN DETECTING BRAIN METASTASES

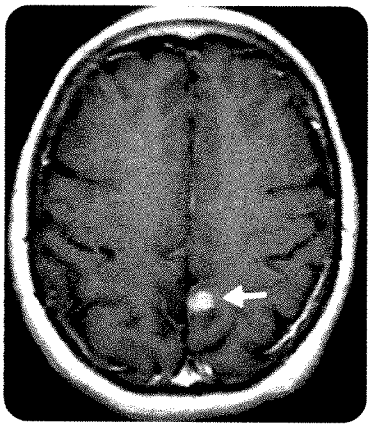


Figure 5. T1-weighted (TR 600/TE 30) image after MAGNEVIST® injection shows an enhancing lesion in left parasagittal region (arrow), as in Figure 1. The high-signal intensity lesion seen in Figure 3 does not enhance. This finding is consistent with chronic small-vessel ischemic disease, not with metastatic disease.

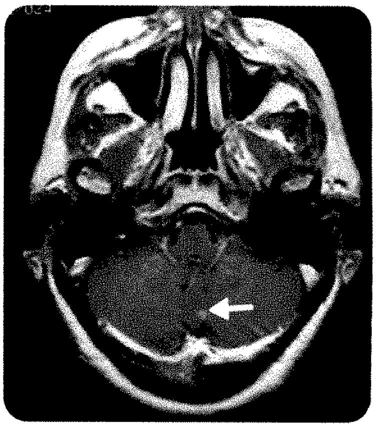


Figure 6. T1-weighted (TR 600/TE 30) enhanced image taken through posterior fossa shows well-delineated lesion in the inferior aspect of the vermis (arrow). Lesion was not clearly appreciated on unenhanced MRI or contrast CT studies.

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☐ **INCREASES DETECTION OF INTRACRANIAL LESIONS**

May detect additional and often smaller lesions than seen with either contrast-enhanced CT or unenhanced T2-weighted images[1,2]

☐ **DETECTION OF ADDITIONAL LESIONS MAY ALTER THERAPY**

MAGNEVIST® injection can increase the radiologic suspicion of metastatic disease, reveal locations more favorable for biopsy, prompt the search for a primary tumor, and modify therapeutic objectives and methods[3]

Magnevist®

(gadopentetate dimeglumine 469.01 mg/mL)

INJECTION

BETTER MEDICINE THROUGH BETTER IMAGES

BERLEX

IMAGING

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.

Well tolerated[4] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCES: **1.** Hinshaw DB Jr, Hasso AN. Gd-DTPA enhances MRI of central nervous system. *Diagnostic Imaging*. 1989;11:90-99. **2.** Price AC, Runge VM, Nelson KL. CNS—neoplastic disease. In: Runge VM, ed. *Enhanced Magnetic Resonance Imaging*. St. Louis: CV Mosby Company; 1989:139-177. **3.** Healy ME, Hesselink JR, Press GA, Middleton MS. Increased detection of intracranial metastases with intravenous Gd-DTPA. *Radiology*. 1987;165:619-624. **4.** Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 µg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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Berlex Laboratories, Inc.
Wayne, New Jersey 07470
60621-6 Revised 7/90 90-890-0051-RV 12/90

BERLEX IMAGING®

POSTHERPETIC NEURALGIA

There Are Many Words To Describe The Pain.

STABBING
PENETRATING
SHARP
JABBING
SHOOTING
UNBEARABLE
PIERCING
GRIPPING
SEARING

And One For Treating It.

Topical
Zostrix®
(Capsaicin 0.025% w/w) Cream

When patients describe the "hurt" of postherpetic neuralgia (PHN), they use a wide range of words to describe a pain that is often intractable and difficult to treat. Zostrix® (Capsaicin 0.025% w/w) Cream provides an effective topical treatment that alleviates intense pain in most PHN patients.

Topical Zostrix Works Where It Hurts

Zostrix®

(Capsaicin 0.025% w/w) Cream

Topical Analgesic

TARGETED ACTION

Acts on sensory nerves at site of application by selectively depleting substance P, a chemomediator of pain impulses along neuropathways.

EFFECTIVE

Alleviates the intense pain associated with postherpetic neuralgia in most patients. May also benefit patients when added to existing systemic drug regimens.

SAFE

No known interactions with systemic medications commonly prescribed for geriatric patients.

Topical Zostrix Works Where It Hurts

DESCRIPTION

Zostrix Cream contains capsaicin, 0.025% w/w, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

INDICATION

Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with rheumatoid arthritis and osteoarthritis.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken or irritated skin. Do not bandage tightly. If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

Adults and children 2 years of age and older: Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

HOW SUPPLIED

1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)

Store at room temperature.
U.S. Patent Nos. 4486450 and 5536404

Marketed by **GENDERM**® Corporation
Northbrook, IL 60062

Calendar

CALENDAR OF MEETINGS

1991		
Jan	18-19	Annual Meeting of the American Academy of Pain Medicine, Clarion Castle Hotel and Resort, Miami Beach, Fla. Contact American Academy of Pain Medicine, 5700 Old Orchard Rd, First Floor, Skokie, IL 60077-1024; (708) 965-2776.
	20-26	18th Annual Meeting of the Southern Clinical Neurological Society, Camino Real Hotel, Cancun, Mexico. Contact Millie F. Walden, Executive Secretary, 3425 SW Second Ave, Suite 154, Gainesville, FL 32607; (904) 373-9765.
	31-Feb 2	14th annual course, "Neurology for Nonneurologists," Omni San Diego (Calif) Hotel. Contact Edith S. Bookstein, Neurology for Nonneurologists, PO Box 2586, La Jolla, CA 92038; (619) 454-3212.
Feb	2-3	Sixth Annual Neuroradiology Review Course, Hyatt Regency, Bethesda, Md. Contact Wendy S. Baker, Course Coordinator, Armed Forces Institute of Pathology, Washsington, DC 20306-6000; (202) 576-2162.
	2-9	Second Annual Clinical Magnetic Resonance Imaging Meeting, Marriott's Mark Resort, Vail, Colo. Contact Program Coordinator, Department of Radiology, Program Committee, Box 17241, Tampa, FL 33682-7241; (813) 873-2090 or (800) 338-5901.
	8-10	"Clinical Neurology for Psychiatrists," Bahia Mar Resort, Ft Lauderdale, Fla. Contact Office of Continuing Medical Education, Albert Einstein College of Medicine / Montefiore Medical Center, 111 E 210th St, Bronx, NY 10461; (212) 920-6676.
	14-16	Annual Meeting of the Western Electroencephalographic Society, Portland Ore. Contact Bonnie Becker, Executive Secretary, Good Samaritan Hospital, Suite 400, 1040 NW 22nd Ave, Portland, OR 97210; (503) 229-7721.
	15-17	Sixth Meeting of The International Study Group of the Pharmacology of Memory Disorders Associated with Aging, Zurich, Switzerland. Contact Professor Richard J. Wurtman, Bldg E25-604, Whitaker College, Massachusetts Institute of Technology, Cambridge, MA 02139.
	15-17	The 24th Annual Recent Advances in Neurology, San Francisco, Calif. Contact Extended Programs in Medical Education, University of California, Room C-124, San Francisco, CA 94143-0742; (415) 476-4251.
	18-20	Fifth International Symposium on Intracranial Hemodynamics: Transcranial Doppler and Cerebral Blood Flow and Other Modalities, Hyatt Regency Embarcadero Center, San Francisco, Calif. Contact Conference Coordinator, Institute of Applied Physiology and Medicine, 701 16th Ave, Seattle, WA 98122; (206) 442-7330.
	20-23	"The Practicing Physician's Approach to the Difficult Headache Patient," Wyndham Hotel, Palm Springs, Calif. Contact Ms Idell Applebaum, Diamond Headache Clinic Research and Educational Foundation, 5252 N Western Ave, Chicago, IL 60625; (312) 878-5558.
	22-24	"Clinical Neurology for Psychiatrists," Fisherman's Wharf Holiday Inn, San Francisco, Calif. Contact Office of Continuing Medical Education, Albert Einstein College of Medicine / Montefiore Medical Center, 111 E 210th St, Bronx, NY 10461; (212) 920-6676.
March	7-9	"Recent Advances in Geriatric Medicine, New Treatment Options for Old Problems," The Pan Pacific Hotel, San Diego, Calif. Contact Cass Jones, Professional Conference Management Inc, 7916 Convoy Ct, San Diego, CA 92111; (619) 565-9921.
	14-16	"Brain Chemistry and Behavior: Advances in Positron Emission Tomography and Single Photon Emission Tomography Imaging," Baltimore, Md. Contact Patty Campbell, Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-3839.
	16-20	Fifth Annual Magnetic Resonance Imaging Conference, Marriott's Camelback Inn, Scottsdale, Ariz. Contact Kevin King, Education Coordinator, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 West Thomas Rd, Phoenix, AZ 85013; (602) 285-3956.
	17-23	24th Latin American Congress of Neurosurgery, Miami, Fla. Contact Sergio Gonzalez-Arias, MD, 8950 N Kendall Dr, Suite 406, Miami, FL 33176; (305) 271-6159.
	18-20	"Spectrum of Developmental Disabilities: Cerebral Palsy: Issues of Early Detection and Intervention," The Johns Hopkins Medical Institutions, Baltimore, Md. Contact Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Bldg, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-2959.
	21-33	"Recent Advances in Neurology and Neurosurgery," Scottsdale, AZ. Contact Toby A. Jardine, Manager, Administration, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix, AZ 85013; (602) 285-3178.
April	10-11	The Second Annual Postgraduate Electromyography Review Course, Iowa City, Iowa. Contact Deborah L. Hatz, Program Coordinator, University of Iowa College of Medicine, Iowa City, IA 52242; (319) 335-8598.
	21-27	43rd Annual Meeting of the American Academy of Neurology, Hynes Convention Center, Boston, Mass. Contact American Academy of Neurology, 2221 University Avenue SE, Suite 335, Minneapolis, MN 55414; (612) 623-8115.
	21-27	American Academy of Neurology Annual Meeting, Hynes Convention Center, Boston, Mass. Contact American Academy of Neurology, 2221 University Ave SE, Suite 335, Minneapolis, MN 55414; (612) 623-8115.
	22	The Annual Meeting of the World Federation of Neurology Research Group on Neuroepidemiology, Boston, Mass. Contact Gustavo C. Román, Chief, Neuroepidemiology Branch, Federal Building, Room 714, 7550 Wisconsin Ave, National Institutes of Health, Bethesda, MD 20892; (301) 496-1714.
May	7-10	Ecuadoran Society of Neurology, Quito, Ecuador. Contact Ecuadoran Society of Neurology, PO Box 2821, Quito, Ecuador.

Instructions for Authors

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Designate one author as correspondent and provide his address and telephone number. Order reprints at the time the typescript is returned after editorial processing. Specify address to which requests for reprints should be sent.

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Refer to patients by number (or, in anecdotal reports, by fictitious given names). Real names or initials should not be used in the text, tables, or illustrations.

Titles.—Titles should be short, specific, and clear. They should not exceed 42 characters per line, including punctuation and spaces, and be limited to two lines, if possible. The title page should include the full names and academic affiliations of all authors, the address to which requests for reprints should be sent, and, if the manuscript was presented at a meeting, the name of the organization, place, and date on which it was read.

Style of Writing.—The style of writing should conform to acceptable English usage and syntax. Slang, medical jargon, obscure abbreviations, and abbreviated phrasing are to be avoided.

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Abstract.—Provide an abstract (135-word maximum) of the article, including statements of the problem, method of study, results, and conclusions. The abstract replaces the summary.

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AMA Manual of Style.—This 1988 edition, formerly the *Manual for Authors & Editors*, is available from Williams & Wilkins, 428 E Preston St, Baltimore, MD 21202. Single copy price: $26.95. A shipping charge is added on all orders not prepaid. If additional ordering information is needed, or to order by telephone, call 1-800-638-0672.

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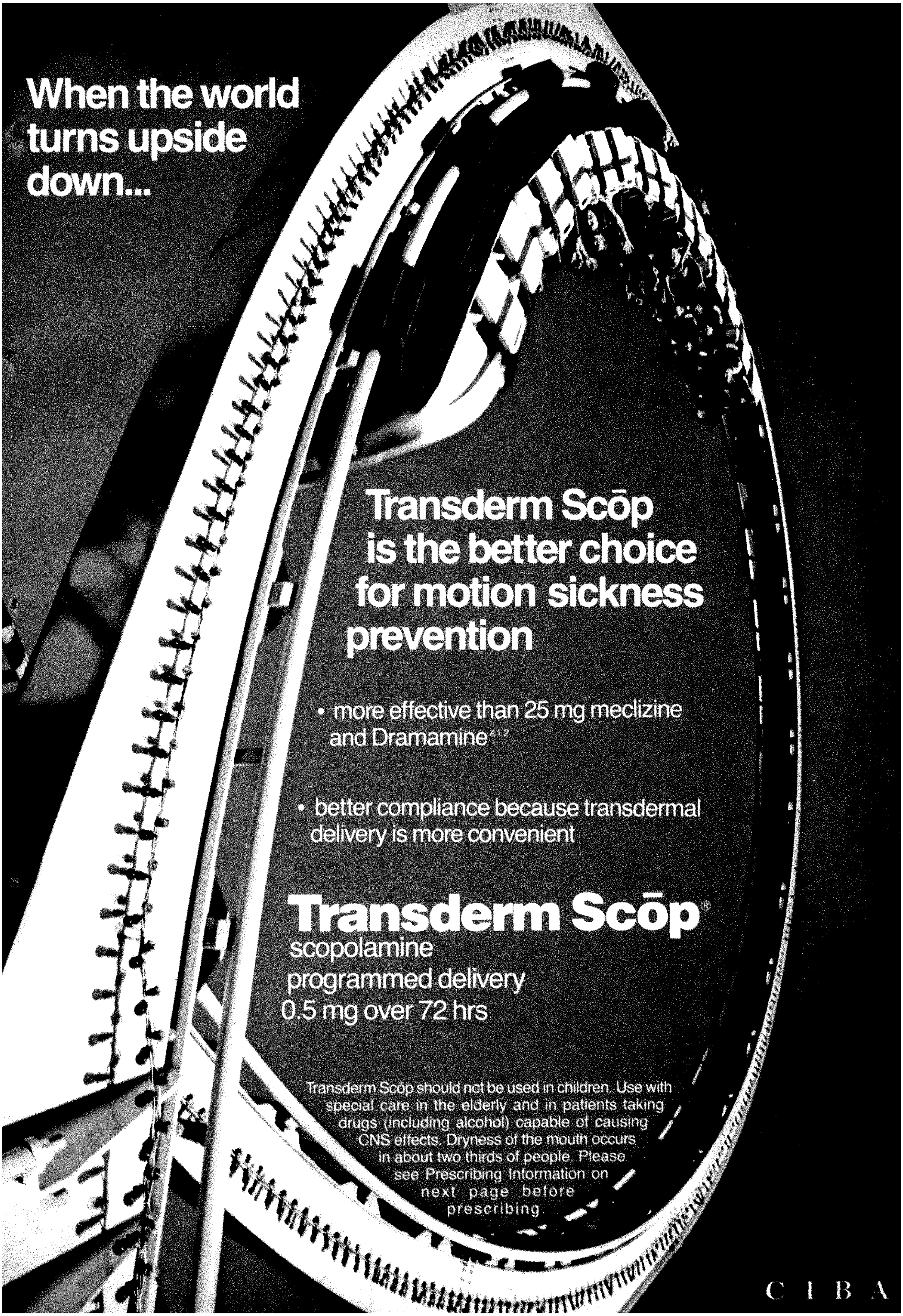

When the world turns upside down...

Transderm Scōp is the better choice for motion sickness prevention

- more effective than 25 mg meclizine and Dramamine®[1,2]
- better compliance because transdermal delivery is more convenient

Transderm Scōp®
scopolamine
programmed delivery
0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

CIBA

Transderm Scōp®

scopolamine

(formerly Transderm-V)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

Dist. by:
CIBA Consumer Pharmaceuticals
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Summit, NJ 07901

C88-5 (Rev. 2/88)

CIBA

References:

1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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INDEX TO ADVERTISERS

American Academy of Clinical Neurophysiology 6
The American Neurological Association 99-100
American Society of Neuroimaging 4

Berlex Imaging 8A-B, 9-10

Ciba Pharmaceutical Company 15-16, 59-60
Columbia University 8
Comprehensive Headache Clinic 111

Downstate Headache Center 6
Du Pont Pharmaceuticals 84-86

Gate Pharmaceuticals 71-72
Geigy Pharmaceuticals 80A-B
GenDerm Corporation 11-12

Eli Lilly & Company 16A-D

Miles Pharmaceuticals 53-54

Osler Institute 116

Parke-Davis .... 64A-B, 65, Cover 3-Cover 4

Sandoz Pharmaceuticals Cover2-2, 78-80, 92-94

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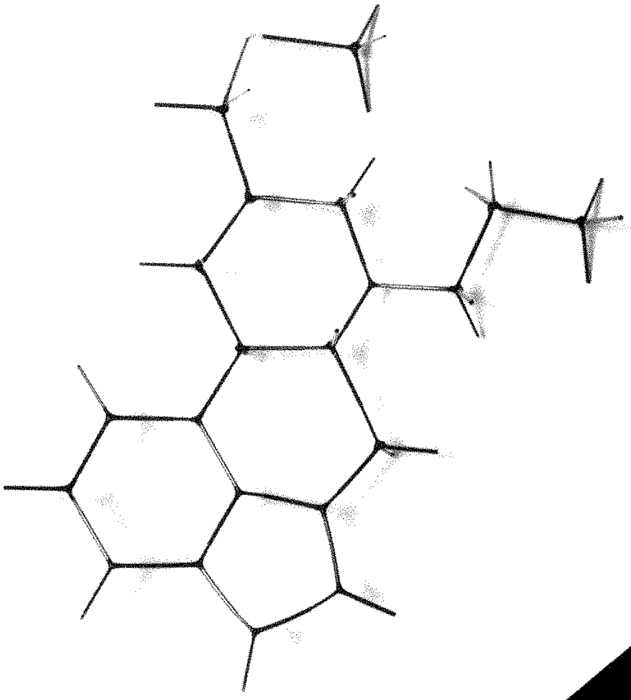
pergolide mesylate

An adjunct to levodopa/carbidopa treatment
in the management of patients
with Parkinson's disease



For more information about Perm
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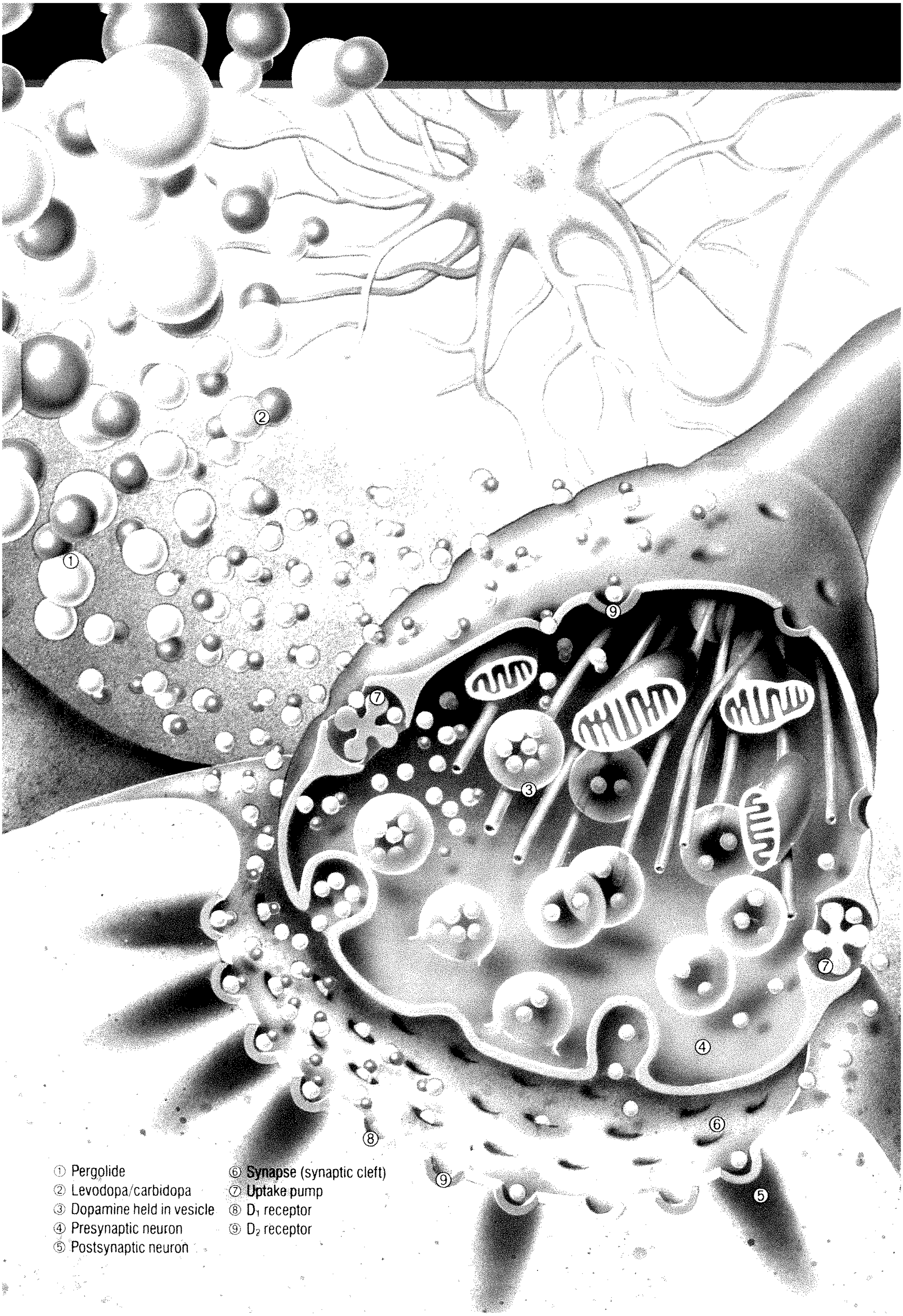
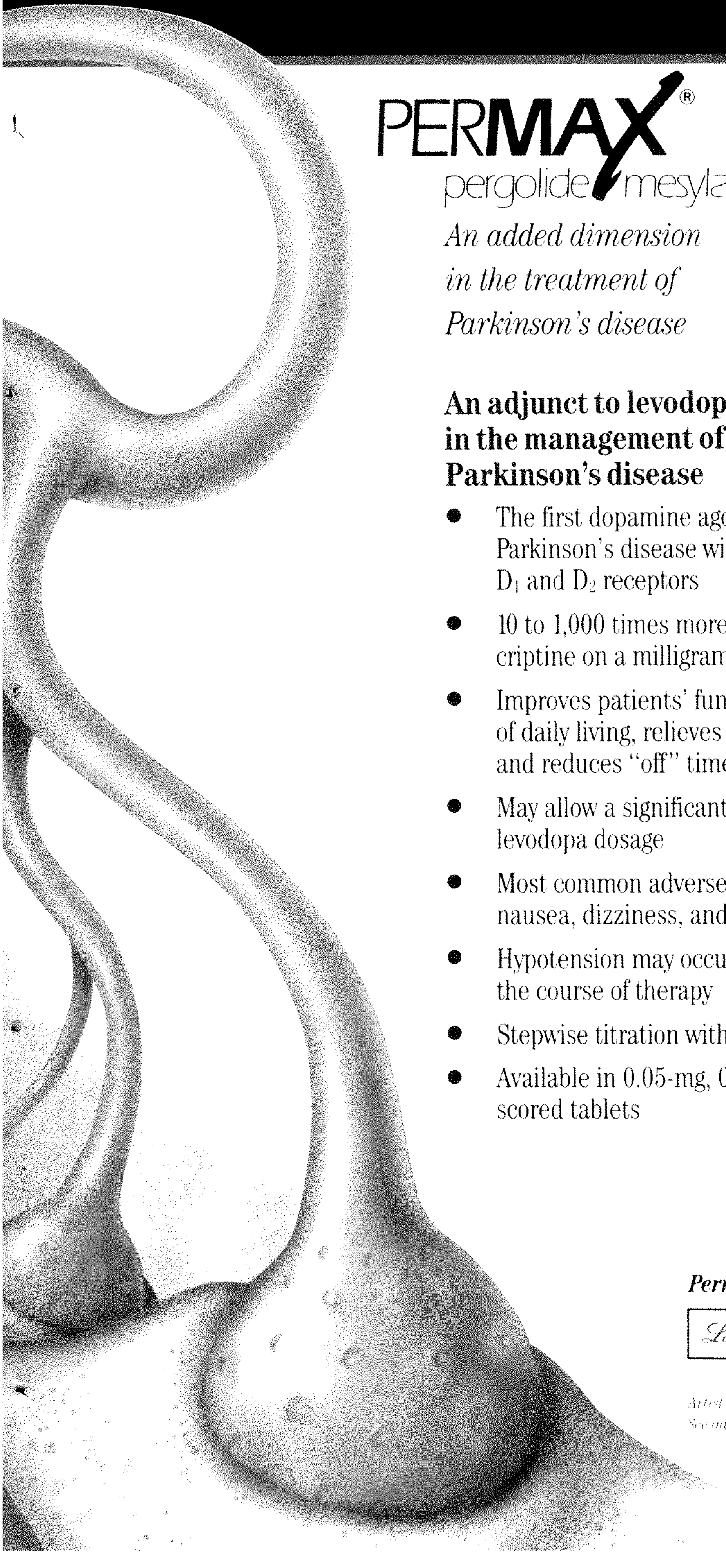


① Pergolide
② Levodopa/carbidopa
③ Dopamine held in vesicle
④ Presynaptic neuron
⑤ Postsynaptic neuron
⑥ **Synapse** (synaptic cleft)
⑦ **Uptake** pump
⑧ D_1 receptor
⑨ D_2 receptor



PERMAX®

pergolide mesylate

An added dimension
in the treatment of
Parkinson's disease

An adjunct to levodopa/carbidopa in the management of patients with Parkinson's disease

- The first dopamine agonist indicated for Parkinson's disease with activity at both D_1 and D_2 receptors
- 10 to 1,000 times more potent than bromocriptine on a milligram-per-milligram basis
- Improves patients' functioning in activities of daily living, relieves signs and symptoms, and reduces "off" time
- May allow a significant reduction in levodopa dosage
- Most common adverse events were dyskinesia, nausea, dizziness, and hallucinations
- Hypotension may occur, especially early in the course of therapy
- Stepwise titration without regard to meals
- Available in 0.05-mg, 0.25-mg, and 1-mg scored tablets

Permax performs

Lilly

Artist's conception of dopaminergic agonism at the synapse
See adjacent page for prescribing information.

Permax*

pergolide mesylate

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to levodopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the sample of patients evaluated had been on levodopa/carbidopa for 3.9 years (range, two days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of levodopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities - *See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Events	
Body System/ Adverse Event*	Pergolide Mesylate N = 189	Placebo N = 187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	
Dyspnea	4.8	
Epistaxis	1.6	
Hiccup	1.1	
Skin and Appendages		
Rash	3.2	
Sweating	2.1	
Special Senses		
Abnormal vision	5.8	
Diplopia	2.1	
Taste perversion	1.6	
Eye disorder	1.1	
Urogenital System		
Urinary frequency	2.7	
Urinary tract infection	2.7	
Hematuria	1.1	

*Events reported by at least 1% of patients receiving pergolide mesylat
included.

Events Observed During the Premarketing Evaluation of Permax —Th
tion reports event frequencies evaluated as of October 1988 for adverse
ocurring in a group of approximately 1,800 patients who took multiple d
pergolide mesylate. The conditions and duration of exposure to pe
mesylate varied greatly, involving well-controlled studies as well as exp
in open and uncontrolled clinical settings. In the absence of appropria
trols in some of the studies, a causal relationship between these ever
treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in te
their relative frequency of reporting in the data base. Events of major
importance are also described in the Warnings and Precautions sectio

The following definitions of frequency are used: frequent adverse eve
defined as those occurring in at least 1/100 patients; infrequent adverse
are those occurring in 1/100 to 1/1,000 patients; rare events are those
ring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, a
inal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infre*
facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia,
pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare*
abdominal syndrome, LE syndrome.

Cardiovascular System —*Frequent:* postural hypotension, syncope,
tension, palpitations, vasodilatations, congestive heart failure; *Infre*
myocardial infarction, tachycardia, heart arrest, abnormal electrocardi
angina pectoris, thrombophlebitis, bradycardia, ventricular extrasy
cerebrovascular accident, ventricular tachycardia, cerebral ischemia
fibrillation, varicose vein, pulmonary embolus, AV block, s
Rare: vasculitis, pulmonary hypertension, pericarditis, migraine, heart
cerebral hemorrhage.

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhe
stipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver f
tests, increased appetite, salivary gland enlargement, thirst, gastroen
gastritis, periodontal abscess, intestinal obstruction, nausea and vo
gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach
melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis,
ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis,
cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes
tus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leuko
lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megalot
anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thr
cythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System —*Frequent:* peripheral edema,
loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycem
deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:*
trolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia;
quent: bone pain, tenosynovitis, myositis, bone sarcoma, arthritis,
osteoporosis, muscle atrophy, osteomyelitis.

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations,
sion, somnolence, insomnia, dystonia, paresthesia, depression, a
tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal d
incoordination, psychosis, personality disorder, nervousness, choreoa
sis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisi
ropathy, neuralgia, hypertonia, delusion, convulsion, libido incre
euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma
thy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, tort
meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia;
stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis,
edema, myelitis, hallucinations and confusion after abrupt discontinuat

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, phary
cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis,
alteration, hemoptysis, asthma, lung edema, pleural effusion, lary
emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fib
larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequen*
discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carci
seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, h
zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule
benign neoplasm, lichenoid dermatitis.

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media
junctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glau
eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cat
retinal detachment, retinal vascular disorder.

Urogenital System —*Frequent:* urinary tract infection, urinary frequ
urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, b
pain, menorrhagia, impotence, cystitis, urinary retention, abortion, v
hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lact
uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menop
kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea,
der carcinoma, breast engorgement, epididymitis, hypogonadism, leuko
nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleedin

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Additional information available to the profession on request.

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Letters to the Editor

Letters to the editor should be submitted as an original and two duplicates. They should be typewritten double-spaced on plain bond paper; they will be subject to editing. If they are prepared on a word processor, do not justify the right margin. A copyright transmittal letter signed by all authors must accompany this (see "Instructions for Authors").

Migraine With Vasospasm and Delayed Intracerebral Hemorrhage

To the Editor.—Cole and Aubé[1] suggested that, in severe migraine attacks, vasospasm may result in ischemic necrosis of intracranial vessel walls, leading to a subsequent vessel rupture responsible for delayed lobar intracerebral hemorrhage, when perfusion pressure is restored. They stated that, except migraine, "subarachnoid hemorrhage, cerebral trauma, central nervous system infection, drug abuse, toxemia, fibromuscular dysplasia, carotid artery dissection, and cerebral vasculitis have all been associated with the radiographic appearance of spasm of the cerebral arteries." Another possible cause for vasospasm is cerebral embolism. We recently described rupture of the arterial wall in two cases of cerebral embolism.[2] One patient suffered a frontal hematoma. As proposed by Villaret et al,[3] arterial spasm may have occurred at the time of cerebral embolism. The morphological expressions specific to cerebral vasospasm are unknown. Cole and Aubé[1] suggested rupture of the arterial wall, secondary to ischemic necrosis. We[2] have had the opportunity to demonstrate such a rupture at the level of an embolic occlusion, preventing any substantial narrowing of the arterial lumen. The resulting local and violent arterial spasm lead to rupture of the vessel wall. No ischemic necrosis was seen. Whatever the underlying mechanism, rupture of the arterial wall must be considered when intracerebral hemorrhage is associated with any potential cause of cerebral vasospasm.

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1. Cole AJ, Aubé M. Migraine with vasospasm and delayed intracerebral hemorrhage. *Arch Neurol.* 1990;47:53-56.
2. Brucher JM, De Smet YD, Gonsette RE. Rupture of the arterial wall in two cases of recent cerebral embolism: morphological expression of cerebral vasospasm? *J Neurol.* 1986;223:267-270.
3. Villaret M, Cachera R, Fauvert R. Spasmes des artères cérébrales provoqués par l'embolie expérimentale du cerveau. *C R Soc Biol (Paris).* 1937;125:58-61.

Migraine and Intracerebral Hemorrhage

To the Editor.—Intracerebral hemorrhage in migrainous patients has only rarely been reported.[1-7] Cole and Aubé[8] recently described three women with lobar intracerebral hemorrhage either during or immediately following typical migraine attacks. The patients did not have evidence of underlying conditions predisposing to intracerebral hemorrhage. The authors suggested vasospasm with necrosis of the vessel wall followed by sudden reperfusion as the cause of rupture of ischemic vessels, resulting in hemorrhage. Clinically, they observed that a migraine attack associated with bleeding was similar to the patient's usual headaches, but somewhat more severe and prolonged. Furthermore, in two patients carotidynia was observed.

We previously described 11 migrainous patients with intracerebral hemorrhage associated with migraine attacks.[9] All of the patients were diagnosed by computed tomographic scan and studied by carotid angiography, cranial magnetic resonance imaging, or both. The mean age was 35.8 years (range, 19 to 48 years). Nine subjects were women, four had a family history of migraine. Six subjects suffered classic migraine and five common migraine. In 10 patients we found the following predisposing conditions for hemorrhage: hypertension in five, vascular malformations in four, and alcoholism in one. In a 31-year-old woman with common migraine, who suffered a right capsular hemorrhage, we failed to find any underlying condition predisposing to bleeding. In seven patients neurologic manifestations due to intracerebral bleeding occurred more than 10 hours after headache started. All the patients presented with a headache similar to the previous attacks, but strikingly more severe.

In conclusion, intracerebral hemorrhage associated with a migrainous headache attack is usually associated with preexisting vascular anomalies. According to Cole and Aubé,[8] in cases without underlying conditions for intracerebral bleeding, severe vasospasm causing vessel wall necrosis may be a reasonable explanation for vascular rupture and hemorrhage during reperfusion. Furthermore, vessels previously debilitated by some diseases, like hypertension or alcoholism, may be prone to rupture during vasomotor and ischemic events in migraine.

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1. Fitzsimons RB, Wolfenden WH. Migraine coma: meningitic migraine with cerebral oedema associated with a new form of autosomal dominant cerebellar ataxia. *Brain.* 1985;108:555-577.
2. Dunning HS. Intracranial and extracranial vascular accidents in migraine. *Arch Neurol Psychiatry.* 1942;48:396-406.
3. Dorfman LJ, Marshall WH, Enzmann DR. Cerebral infarction and migraine: clinical and radiologic correlations. *Neurology.* 1979;29:317-322.
4. Selby G, Fryer JA. Fatal migraine. *Clin Exp Neurol.* 1984;20:85-92.
5. Guest IA, Woolf AL. Fatal infarction of brain in migraine. *B M J.* 1964;1:225-226.
6. Vázquez-Cruz J, Arboix-Damunt A, Martí-Fábregas J. Hemorragia cerebral en la migraña complicada: presentación de dos casos. *Neurología.* 1986;1(suppl 1):74.
7. Cole AJ, Aubé M. Late-onset migraine with intracerebral hemorrhage: a recognizable syndrome. *Neurology.* 1987;37(suppl 1):238.
8. Cole AJ, Aubé M. Migraine with vasospasm and delayed intracerebral hemorrhage. *Arch Neurol.* 1990;47:53-56.
9. Vázquez-Cruz J, Alvarez-Sabín J, Molins-Albanell A, Titus F, Codina A. Hemorragia cerebral en la migraña complicada: estudio de 11 casos. *Neurología.* 1989;4:157.

In Reply.—De Smet and Brucher point out that two cases of intracerebral hemorrhage, both diagnosed at postmortem examination, appear to have been the result of arterial rupture following embolic occlusion. They propose that such rupture may be the consequence of local violent vasospasm following embolic occlusion. While our list of potential causes of cerebral vasospasm was not meant to be exhaustive, we would emphasize that none of our patients had evidence of embolic arterial occlusion demonstrated by acute angiographic studies.

Vazquez-Cruz has called our attention to his report of 11 patients with migraine who suffered intracerebral hemorrhage. Nine of those patients had hypertension or identified vascular malformations, one was an alcoholic, and one had no predisposing cause. We are unaware of an association between alcoholism and intracerebral hemorrhage except in the setting of coagulopathy or direct trauma. None the less, none of our patients were alcoholics. Migraine is a common disorder, and it is likely that a significant number of patients who sustain intracerebral hemorrhage, from whatever cause, also suffer from migraine. The point of our report was to emphasize that, in a number of patients without other identifiable cause for intracerebral hemorrhage, migraine itself may be causative. We suspect that Dr Vazquez's last case may fit into this group.

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Isopropyl Alcohol Intoxication

To the Editor.—On reading the article "Isopropyl Alcohol Intoxication" by Rich et al[1] in the March issue of the Archives, I was struck by the fact that in all three of the cases presented there was nothing neurologically unique about these alcoholic subjects. In case 1, the sluggish pupils, prominent horizontal nystagmus, and appendicular and gait ataxia associated with peripheral neuropathy suggests Wernicke's encephalopathy.[2] No mention is made of treatment with thiamine. In case 2, the patient had an alcohol-related seizure and subsequent delirium tremens. I am surprised that a computed tomographic scan of his brain was not performed, given his recent head trauma. In case 3, the coma is consistent with intoxication with isopropyl alcohol, which is well described.[3]

The conclusions about the presentation of isopropyl alcohol intoxication presenting in two distinct patterns (stupor in a known alcoholic or encephalopathy in alcoholic subjects who hide their addiction) is not warranted. The only unique clinical points about isopropyl alcohol are the reflections of its metabolic handling. Unlike ethanol, ethylene glycol, and methanol, isopropyl alcohol causes ketosis without a significant wide-gap metabolic acidosis.[3] The emergent care of patients who may have ingested isopropyl alcohol involves support of the airway and attention to ruling out methanol or ethylene glycol ingestion. Since all three cause a widened osmolar gap, specific levels of ethanol, methanol, and ethylene glycol are necessary in order to make a decision about treating with an ethanol drip. This is not indicated for isopropyl ingestion, but is indicated for methanol and ethylene glycol. Finally, attention to replacement of both thiamine and niacin in any alcoholic with neurologic findings is paramount because the clinical diagnosis of either Wernicke's encephalopathy or alcoholic pellagra is very difficult.[4,5] There is very little toxicity associated with replacement therapy.

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1. Rich J, Scheife RT, Katz N, Caplan LR. Isopropyl alcohol intoxication. *Arch Neurol.* 1990; 47:322-324.
2. Harper CG, Giles H, Finlay-Jones R. Clinical signs in the Wernicke-Korsakoff complex. *J Neurol Neurosurg Psychiatry.* 1986;49:341-345.
3. LaCouture PG, Wason S, Abrams A, Lovejoy FH. Acute isopropyl alcohol intoxication. *Am J Med.* 1983;75:680-686.
4. Lindboe CF, Loberg EM. The frequency of brain lesions in alcoholism. *J Neurol Sci.* 1988; 88:107-113.
5. Serdaru M, Hausser-Hauw C, Laplane D, et al. The clinical spectrum of alcoholic pellagra encephalopathy. *Brain.* 1988;111:829-842.

In Reply.—We agree with Dr Wrenn that identification of the specific offending alcohol is important in managing patients with acute intoxications. One purpose of our report was to alert readers to the laboratory findings in patients with acute isopropyl alcohol intoxication, a disorder that we believe is common, yet little appreciated. Unfortunately, many breathalyzer tests as well as a newly introduced "saliva alcohol dipstick" method[1] do not distinguish between alcohols. We agree with his comments about management of the acute intoxications, including generous administration of thiamine in these patients, many of whom also abuse ethanol and eat sparingly and poorly.

Among the intoxicant alcohols (ethanol, methanol, isopropyl alcohol, ethylene glycol) isopropyl alcohol and ethanol are the only ones that are repeatedly and deliberately ingested for prolonged periods. The chronic effects of isopropyl alcohol are thus important. We are pleased to know that Wrenn's neurological experience in emergency medicine is extensive enough that he can chide us on the neurological uniqueness of our case 1, the only patient with chronic isopropyl alcohol use. Wrenn thinks the patient's findings are not separable from Wernicke's encephalopathy. During the senior author's (L.R.C.) training at the Boston (Mass) City Hospital and since, he has seen well over 100 patients with Wernicke's encephalopathy and is very familiar with the findings. In Wernicke's encephalopathy, the signs develop rapidly and are not due to a direct effect of ethanol or any other toxic agent on the nervous system and do not respond quickly to abstinence. The ocular findings may respond within hours to days to thiamine, but the other signs resolve more slowly or not at all. Our patient had the gradual onset of a constellation of signs that indicated diffuse cerebral, pyramidal tract, and cerebellar dysfunction that disappeared within 4 days of stopping isopropyl alcohol ingestion. He had received thiamine at the Boston City Hospital 3 weeks before and had been eating very well at his sister's house since then. His neurologic signs indicated subacute isopropyl alcohol toxicity and not Wernicke's encephalopathy. No other examples of subacute or chronic isopropyl alcohol intoxication have been reported to our knowledge, but we are confident that readers will now be able to identify such patients now that they are alerted to their presence and the findings.

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1. Rodenberg H, Bennet J, Watson WA. Clinical utility of a saliva alcohol dipstick estimate of serum ethanol concentrations in the emergency department. *Ann Pharmacother.* 1990:24:358-361.

Seizures After Stroke

To the Editor.—The study of epilepsy in stroke by Kilpatrick et al[1] probably represents the largest study to date of a topic that has been largely neglected.

However, we found the quality of data obtained rather disappointing. For instance, surely the authors should have strived to obtain complete electroencephalographic documentation of these patients, both with and without seizures. Conclusions drawn from electroencephalograms in the seizure group only are incomplete without a comparison with the nonseizure group, and even in these, only 26 of 44 patients had had electroencephalograms.

Similarly, in the 310 patients with cortical infarcts who were evaluated, 118 (38%) had "inadequate investigations." This is a surprisingly large number for a prospective study. Surely this huge unknown group invalidates any conclusions? Also, the authors seem to have lost 60 patients (the difference in totals between Tables 1 and 2).

Four of the 44 patients within the seizure group had previous epilepsy, but we could not find how many in the nonseizure group (956 patients) had previous seizures. Surely this is a relevant and critical omission?

In conclusion, we are disappointed by the degree of incompleteness of data collection, considering this was a prospective study. This criticism applies particularly to the nonseizure group, which should have acted as a large control group for comparison. The percentages of patients receiving the various investigations is not stated. The number that received computed tomographic scans (90%) is particularly disappointing. Clearly there are logistical problems in a large study of this kind, but if the quality of data collection falls below a certain level (only 62% were adequately investigated and age and sex ratios are not included), conclusions may give an unjustified sense of accuracy.

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1. Kilpatrick CJ, Davis SM, Tress BM, Rossiter SC, Hopper JL, Vandendreisen ML. Epileptic seizures in acute stroke. *Arch Neurol.* 1990;47:157-160.

In Reply.—In reply to the letter from Zhu and Norris, we wish to make the following comments.

While we would accept that our large, prospective, clinical study has some limitations, we believe the data collected justify the conclusions made.

This study did not aim to assess the value of the electroencephalogram in predicting the risk of developing seizures in acute stroke. Clearly, electroencephalograms were not obtained from all patients, and we drew no conclusions from the electroencephalographic data collected.

The sex ratio of patients with seizures was the same as those without seizures (55% male, 45% female), and there was no significant difference in the mean age of patients with seizures (62 ± 10 years) and those without seizures (66 ± 15 years).

Table 2 does not list the pathogenesis of all cortical infarcts but only those pathogeneses associated with seizures, hence the difference between the total number of patients with carotid territory cortical infarcts in Table 1 and Table 2.

In this study, 118 (32%) of 370 cortical infarcts had unknown pathogenesis due to inadequate investigation. These patients had severe neurological deficits and no clear clinical signs of either a cardioembolic source or large-vessel atherosclerosis. It has been the practice in our institution not to routinely investigate the carotid circulation in those patients with clinical evidence of extensive infarction where carotid endarterectomy would not be contemplated. Overall, 40% of patients with cortical infarction were investigated with either digital subtraction angiography or carotid duplex scanning. As stated in the text, we were well aware of the large number of patients in whom the pathogenesis was unknown, often due to therapeutically appropriate but diagnostically inadequate investigation. We were, therefore, very cautious in making conclusions regarding the pathogenesis of cortical infarcts and the development of seizures.

Although we agree that ideally all patients with stroke or transient ischemic attacks should have a computed tomographic scan, in this study all patients with seizures had a computed tomographic scan and the overall computed tomographic scan rate of 90% is comparable with other stroke registries.[1]

We agree that it would be of interest to know the number of patients in the nonseizure group who had a history of epilepsy; however, this study did not aim to assess the association between cerebrovascular disease and a history of epileptic seizures. The history of epilepsy in four of the 44 patients with seizures complicating stroke was included as a possible precipitating factor.

As stated by Drs Zhu and Norris, the subject of epileptic seizures and acute stroke has received relatively little attention in the literature. Further studies to confirm our findings and, in particular, to assess the risk of recurrent seizures in these patients with acute seizures are needed.

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1. Kunitz SC, Gross CR, Heyman A, et al. The pilot stroke data bank: definition, design, and data. *Stroke.* 1984;15:740-746.

Is Radiosurgery All That It Appears to Be?

To the Editor.—We were rather shocked by the publication entitled "Stereotactic Gamma Knife Radiosurgery, Initial North American Experience in 207 Patients," by Lunsford and coworkers,[1] that appeared in the February 1990 issue of the Archives. The attractiveness of a painless therapy such as radiation appears to have beguiled the authors and editors into overlooking the substantiation of assumptions that were expressed in the abstract of this article.

At the Neurological Institute of New York, we have had extensive experience in all modes of treatment for arteriovenous malformations (AVMs), including microsurgery, embolization, and radiosurgery (linear accelerator). Over the past 10 years, we have evaluated over 600 patients and have operated on, embolized, and recently carried out radiosurgery on these patients. This experience has allowed us to evaluate the characteristics of many AVMs in patients who have come for an opinion on therapy, proposed or already performed.

Thus far, less than three of our patients per year have had AVMs deemed appropriate for radiosurgery on the basis of size and inoperability. Given our annual experience, it is of concern to us that Lunsford and coworkers, using their criteria of "inoperability, failed surgery, and desire of the patient," have treated approximately 85 patients with AVMs per year by radiotherapy. Included in their group must be a large number where the lesions exceeded the size criteria for expected success, or small and superficial lesions that an experienced surgeon could remove with minimal morbidity.

While all of us are striving to advance the treatment of AVM, the implication that radiosurgery is a safer and more effective therapy fails to be confirmed in this article. The data provided in the body of their article does not substantiate their statement in the abstract that radiosurgery is a therapeutically effective alternative to microsurgical removal of AVMs. Of their 113 patients with AVMs, 12 patients were followed up for 1 year. Only five of these patients showed the AVM to be angiographically obliterated, and yet their technique is touted as a viable alternative to microsurgery. Furthermore, our experience with surgery and embolization indicates that it is fallacious to assume that the "angiographic residual" after embolization accurately reflects the true boundary of the AVM.

Lastly, it is yet to be shown that an effective level of radiotherapy applied to an AVM will prove safe in the long term.

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1. Lunsford LD, Flickinger J, Coffey RJ. Stereotactic gamma knife radiosurgery: initial North American experience in 207 patients. *Arch Neurol.* 1990;47:169-175.

In Reply.—The response to our publication that appeared in the February 1990 issue of the Archives is most interesting. The goal of surgical treatment of vascular malformations, whether by microsurgery or by radiosurgery, is the same: total obliteration of an arteriovenous malformation (AVM) with preservation of neurological function, ultimately leading to the elimination of the risk of bleeding. The relative recent availability of radiosurgical techniques in the United States has led to a widespread evaluation of single-fraction, highly focused photon irradiation of AVM that is deemed unsuitable for conventional microsurgical removal. The great risk in radiosurgery (as opposed to microsurgery) is that during the treatment the patient feels nothing and the doctor sees nothing. No physician team involved in radiosurgery should be beguiled by this feature, as the benefits of radiosurgery and the risks do not accrue until later.

Dr Stein indicates that in the past 10 years, he has evaluated and subsequently "operated on, embolized, and recently carried out radiosurgery" on 600 patients with AVM. This is a treatment rate of approximately five patients per month. We treated 113 patients in a 16-month period, ie, seven per month. Between two major tertiary academic medical centers (the University of Pittsburgh [Pa] and Columbia University [New York, NY]) this difference is probably not statistically significant. Because of the known size limitations for radiosurgery and the availability of competent neurosurgeons, we found that the patient population referred to us was already preselected by the referring physicians for small size and/or high risk for surgery. It is further important to point out that, in order to treat 113 patients in the interval reported in our article, more than 400 patients with AVMs were carefully screened by evaluating both clinical indications and radiographic studies. We selected patients for radiosurgery if the AVM was of suitable size for radiosurgery, and microsurgery was felt to be too risky, or was refused by the patient. The opening of the first North American gamma unit at the University of Pittsburgh undoubtedly tapped a storehouse of diagnosed, but previously untreated, AVM. Our referrals have come from neurologists, internists, patients themselves, and more than 50 different neurosurgeons.

All patients are discussed preoperatively at a Combined Arteriovenous Malformation Conference that is held twice a month at the University of Pittsburgh. This conference is attended by neurological surgeons skilled in both microsurgery and radiosurgery, radiation oncologists, radiation physicists, and radiologists. All patients are evaluated as to what modalities will best suit the particular patient (no treatment, embolization, microsurgery, or radiosurgery alone or in combination).

We expect that as Stein and coworkers' experience with radiosurgery increases, they will find more AVMs suitable for radiosurgery. It is also interesting that Stein and coworkers express, on the one hand, concern referable to the field of radiosurgery while, on the other hand, adopt a linear accelerator technique, for which the least amount of long-term data exists as to either safety or efficacy. This is in contrast not only to our North American experience using stereotactic radiosurgery with the gamma unit, but also to the more than 20 years of experience accumulated at sites in Europe and elsewhere. We completely agree that radiosurgery must be thoroughly, scientifically, and rigorously evaluated in order to determine its role vs the alternatives of doing nothing or embolization or microsurgery. Fortunately, in the scientific community of the United States, this is proceeding rapidly. For example, an International Symposium on Radiosurgery was offered last year in Charlottesville, Va, another symposium will be presented in June 1990 in Boston, Mass, and the University of Pittsburgh will host an International Radiosurgical Symposium in June 1991.

The purpose of our article in the Archives was to bring (to the attention of physicians not familiar with radiosurgery) its possible therapeutic potential for treatment of AVMs and brain tumors. Since August 1987, we have treated 239 patients with AVM (7.5 patients per month); our results parallel previous reports, eg, a total AVM obliteration rate of 72% (defined as complete disappearance by angiogram within 2 years). Perhaps Stein and coworkers have read more into our abstract than was printed: "the results were encouraging during the minimum follow-up period of 6 months" . . . "In addition, our initial experience further suggests that stereotactic radiosurgery using the gamma unit is a therapeutically effective and economically sound alternative to microneurosurgical removal of selected intracranial tumors and vascular malformations." Our data then and now support this concept.

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Editorials

P24923

The Pathogenesis of Dermatomyositis

Considerable progress has been made in the understanding of dermatomyositis. Banker and Victor[1] characterized childhood dermatomyositis as an angiopathy in 1966. Banker then identified distinctive capillary endothelial changes and postulated that these were an early and fundamental lesion in dermatomyositis.[2] Subsequently, Carpenter et al[3] showed endomysial capillary necrosis and significantly reduced capillary numbers relative to muscle fiber area, providing substantive support for muscle fiber atrophy being a sequel of chronic sublethal ischemia.

See also p 26.

In this issue of the ARCHIVES, Kissel et al[4] provide still more evidence for the primacy of blood-vessel damage as an early pathologic feature of dermatomyositis. The report by Kissel et al[5] followed up on an earlier study from the same group, which showed that membrane attack complex (MAC) was present on muscle biopsy in blood vessels of patients with dermatomyositis. The present study used quantitative histologic methods, combined with immunofluorescent studies of MAC to show that the presence of MAC in capillaries in certain regions of the muscle was coextensive with muscle fiber damage. Membrane attack complex deposition presumably damaged or occluded vessels. This deposition preceded the wide array of muscle fiber damage that can occur in dermatomyositis.[6] The observations by Kissel and coworkers also support studies that have suggested that inflammation follows, rather than precedes, muscle damage in dermatomyositis.[7,8]

Both the present and previous studies by Kissel's group are based on studies of the C5b-9 complement MAC. Membrane attack complex is the final pathway for both the primary complement cascade, as well as the alternative complement pathway.[9] When the complement cascade is activated, new antigenic sites (neoantigens) are presented and these neoantigens can be detected by immunofluorescent techniques applicable to routine frozen muscle biopsy sections. Membrane attack complex has been identified as important in connective tissue diseases such as systemic lupus erythematosus, and may well contribute, to some extent, to phagocytosis of muscle fibers in conditions not considered primarily inflammatory, such as Duchenne's dystrophy.[10]

The importance of humoral immunity as an early and initiating event in dermatomyositis was suggested by Whitaker and W.K. Engel, who found that IgG, IgM, and complement were deposited in the walls of the muscle capillaries of patients with dermatomyositis.[8] As in the studies by Kissel and coworkers, these changes appeared within vessels that did not have inflammation and appeared normal by light microscopy.[8]

Membrane attack complex is a critical mediator of humoral, immunologic lysis of cell membranes.[9] The studies by Kissel and coworkers corroborate studies published earlier this year by Emslie-Smith and A.G. Engel[11] in which MAC deposition was found in blood vessel walls in dermatomyositis. These authors, using a lectin marker for capillaries, also confirm the earlier findings of Carpenter et al[3] and Carry et al[12] of a reduced number of capillaries relative to muscle fiber area. Taken together, these recent investigations strongly support the thesis that humorally mediated damage to blood vessels initiates the angiopathy of dermatomyositis affecting both capillaries and larger blood vessels. Occlusion of larger blood vessels may lead to actual infarcts.[3]

If, as the studies by Kissel and coworkers suggest, MAC deposition initiates or perpetuates local blood vessel damage, the complement cascade could have been activated by antibody binding to blood vessels as has previously been reported in dermatomyositis.[8] The MAC-containing capillaries occur in clusters.[5,11] This distribution of MAC suggests that complement activation occurs as the result of a pathological process in a larger, more proximal vessel or that a local process in a region of capillaries results in local initiation of the complement cascade.[13] Alternatively, an abnormality in one of the proteins that regulate MAC could be present. The S protein[14] and the complement receptor protein, CR-1,[15] have been found to be abnormal in systemic lupus erythematosus, where MAC appears to be of pathogenic importance.[16] The frequent presence of tubuloreticular structures in endothelial cells may be relevant to MAC deposition.[6]

What inciting factor or process causes antibody deposition and activates the complement cascade? Presently, no definite answer exists. Viral infection is a possibility. It has been supported by a documented case of influenza B virus producing the histopathologic appearance of dermatomyositis.[17] There is also a recent report of picornovirus RNA in the muscle of patients with dermatomyositis, but the localization is to macrophages and not the microcirculation.[17]

The idiopathic inflammatory myopathies are now sufficiently well understood to justify their classification into three major subgroups as follows: dermatomyositis, inclusion body myositis, and polymyositis.[19] There is hope that the pathogenesis and optimal therapy of each of the trio will be completely defined in the foreseeable future. Distinctive clinical features and characteristic muscle pathology now define these disorders. Dermatomyositis usually has a virtually pathognomonic skin rash and equally distinctive changes on nail-fold capillary microscopy.[20] Although the pattern of weakness is not specific, the muscle pathology of dermatomyositis is pathognomonic, although there can be marked regional variability of the severity of the changes.[19]

First recognized in 1971,[21] inclusion body myositis can often be recognized clinically by the relatively frequent distinctive distal weakness involving anterior tibial and wrist flexor muscles and the accompanying severe quadriceps weakness. Later, moderate proximal weakness develops. The distinctive light microscopic features of rimmed vacuoles that contain 15- to 18-nm tubulofilamentous masses define inclusion body myositis.

Idiopathic polymyositis lacks the pathognomonic pathological features that characterize either dermatomyositis or inclusion body myositis, but the presence of partial invasion of nonnecrotic muscle cells by cytotoxic lymphocytes[23] and the presence of conspicuous expression of class I major histocompatibility complex products on the surface of practically all muscle fibers are quite characteristic features.[24] Thus, polymyositis, in contrast to dermatomyositis, appears to be a cell-mediated disease. The clinical and pathological features of idiopathic polymyositis may be indistinguishable from other more specific forms of inflammatory myopathies, such as those associated with human immunodeficiency virus infection, human T-cell lymphotropic virus 1 infection, toxoplasmosis, or Lyme disease.

A number of major questions remain to be clarified with regard to the pathogenesis of dermatomyositis. Of course, the most pressing question is the primary etiology, but other issues are also important. Why are only skin and muscle (and rarely lung and intestines) involved? Is there any role for cell-mediated immunity? What host factors are important in the response to an inciting agent? The importance of this latter question is emphasized by the occurrence of the B8, DR3 histocompatibility antigens with increased frequency in patients with dermatomyositis, by the occurrence of dermatomyositis in identical twins, and by the evidence of specific anti-histidyl antibodies such as JO-1.[25] These antibodies are implicated in individual variations in the course of the illness; JO-1 antibodies are seen in only 20% of all patients with dermatomyositis, but are present in the majority of patients with interstitial inflammatory lung disease complicating dermatomyositis.[25,26]

A major goal of studies elucidating the pathogenesis of the inflammatory myopathies is to suggest new and more effective treatment strategies for dermatomyositis, inclusion body myositis, and polymyositis. Corticosteroids and immunosuppressants are the mainstay of treatment and are effective in virtually all cases of childhood, and many cases of adult, dermatomyositis.[27] Corticosteroids, often considered to have a greater effect on cellular rather than humoral immunity, are more effective in dermatomyositis or polymyositis despite evidence suggesting that humoral mechanisms are more important in dermatomyositis, while cellular mechanisms are implicated in polymyositis and inclusion body myositis.[19,28]

Intravascular deposits of circulating complexes may mediate vascular damage. Immunotherapy with monoclonal antibody can produce clinical remission in other vasculitic disorders.[27] Knowing that vascular damage is an early feature in dermatomyositis may pave the way for better treatment.

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References

1. Banker BQ, Victor M. Dermatomyositis (systemic angiopathy) of childhood. *Medicine.* 1966;45:261-289.

2. Banker BQ. Dermatomyositis of childhood. *J Neuropathol Exp Neurol.* 1975;34:46-75.

3. Carpenter S, Karpati G, Rothman S, Watters G. The childhood type of dermatomyositis. *Neurology.* 1976;26:952-962.

4. Kissel JT, Halterman RK, Rammohan KW, Mendell JR. The relationship of complement-mediated microvasculopathy to the histologic features and clinical duration of disease in dermatomyositis. *Arch Neurol.* 1991;48:26-30.

5. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. *N Engl J Med.* 1986;314:329-334.

6. Carpenter S, Karpati G. *Pathology of Skeletal Muscle.* New York, NY: Churchill Livingstone Inc; 1984.

7. Whitaker JN. Inflammatory myopathy: a review of etiologic and pathogenetic factors. *Muscle Nerve.* 1982;5:573-592.

8. Whitaker JN, Engel WK. Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. *N Engl J Med.* 1972;286:333-338.

9. Kolb WP, Muller-Eberhard HJ. Neoantigens of the membrane attack complex of human complement. *Proc Natl Acad Sci U S A.* 1975;72:1687-1689.

10. Engel AG, Bisecker G. Complement activation in muscle fiber necrosis: demonstration of the membrane attack complex of complement in necrotic fibers. *Ann Neurol.* 1982;12:289-296.

11. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. *Ann Neurol.* 1990;27:343-356.

12. Carry MR, Ringel SP, Starcevich JM. Distribution of capillaries in normal and diseased human skeletal muscle. *Muscle Nerve.* 1986;9:445-454.

13. Pangburn MK, Muller-Eberhard HJ. The alternative pathway of complement. *Semin Immunopathol.* 1984;7:163-192.

14. Podack ER, Muller-Eberhard HJ. Isolation of human S protein, an inhibitor of the membrane attack complex of complement. *J Biol Chem.* 1979;254:9908-9914.

15. Iida K, Mornaghi R, Nussenzweig V. Complement receptor CR-1 deficiency in erythrocytes from patients with systemic lupus erythematosus. *J Exp Med.* 1982;155:1427-1438.

16. Falk RJ, Dalmasso AP, Kim Y, Lam S, Michael A. Radioimmunoassay of the attack complex of complement in serum from patients with systemic lupus erythematosus. *N Engl J Med.* 1985;312:1594-1599.

17. Gamboa ET, Eastwood AB, Hays AP, Maxwell J, Penn AS. Isolation of influenza virus from muscle in myoglobinuric polymyositis. *Neurology.* 1979;29:1323-1325.

18. Rosenberg NL, Rotbart HA, Abzug MJ, Ringel SP, Levin MJ. Evidence for a novel picornavirus in human dermatomyositis. *Ann Neurol.* 1989;26:204-209.

19. Karpati G, Carpenter S. Idiopathic inflammatory myopathies. *Curr Opin Neurol Neurosurg.* 1989;1:806-814.

20. Silver RM, Maricq HR. Childhood dermatomyositis: serial microvascular studies. *Pediatrics.* 1989;83:278-283.

21. Yunis EJ, Samaha FJ. Inclusion body myositis. *Lab Invest.* 1971;25:240-248.

22. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis: a distinct variety of idiopathic inflammatory myopathy. *Neurology.* 1978;28:8-17.

23. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies, IV: cell-mediated cytotoxicity and muscle fiber necrosis. *Ann Neurol.* 1988;23:168-173.

24. Karpati G, Pouliot Y, Carpenter S. Expression of immunoreactive major histocompatibility complex products in human skeletal muscles. *Ann Neurol.* 1988;23:64-72.

25. Love LA. Causes of idiopathic inflammatory myopathy. In: Plotz PH, moderator. Current concepts in the idiopathic inflammatory myopathies: polymyositis, dermatomyositis, and related disorders. *Ann Intern Med.* 1989;111:148-150.

26. Miller FW, Twitty SA, Biswas T, Plotz PH. Origin and regulation of a disease-specific autoantibody response. *J Clin Invest.* 1990;85:468-475.

27. Cronin ME. Treatment. In: Plotz PH, moderator. Current concepts in the idiopathic inflammatory myopathies: polymyositis, dermatomyositis, and related disorders. *Ann Intern Med.* 1989;111:153-155.

28. Mathieson PW, Cobbold SP, Hale G, et al. Monoclonal antibody therapy in systemic vasculitis. *N Engl J Med.* 1990;323:250-254.

Caring for the Uninsured and Underinsured

There is a consensus among nearly all neurologists, as well as other groups of physicians and the general public, that a nation with the resources of the United States should make basic health care (including neurologic care) available to all citizens. At present, there are approximately 31 to 37 million Americans uninsured, including 16% of children under the age of 15 years, even though annual health care expenditures now exceed $600 billion (or 11% of the gross national product).[1] As the burden of paying for the excellence and excesses of our health system increases, the system's dropouts are mainly poor people and inner city hospitals. For example, patient encounters with physicians are 15% greater for white than for black citizens, even though twice as many blacks perceive their own health as fair or poor.[2]

In the spring of 1991, the *Journal of the American Medical Association* and the nine specialty journals of the American Medical Association will devote a portion of a special theme issue to "Caring for the Uninsured and Underinsured".[3] Since the *Journal of the American Medical Association* itself will address the financial aspects of care, the ARCHIVES is especially interested in contributions that reflect the authors' views concerning existing barriers to the care provided by neurologists, and what can be done about it. Many neurologists have expressed such views informally, and many professional organizations have discussed these vital issues. The American Medical Association is now providing an opportunity for groups and individuals to speak for the record. The ARCHIVES will submit contributions for peer review for possible publication in the "Practice of Neurology" section.

The astonishing advances in the diagnosis and treatment of many neurologic disorders during the past 30 years create a social imperative for neurologists and other physicians to be able to serve all people, to help devise ways to improve the health of our nation's downtrodden, to work toward equity for all groups in society, and to do everything possible to eliminate the morbidity and suffering of neglected neurologic disorders—yet without a wasteful "shotgun" approach to care that society can no longer afford. Clearly, past successes can create future failures, because so much more can now be done. The national community of neurologists must not let this happen.

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References

1. Levit KR, Freeland MS, Waldo DR. National health care spending trends: 1988. *Health Aff.* Summer 1990:171-184.
2. National Center for Health Statistics. *Health, United States, 1989.* Hyattsville, Md: Public Health Service, 1990:3.
3. Lundberg GL, Blendon RJ. A special *JAMA* theme issue on caring for the uninsured and the underinsured. *JAMA.* 1990;264:739.

1990 Reviewers

Yearly recognition is small recompense for our reviewers of articles submitted to the Archives. It is impossible to estimate the time and effort expended by you in helping us make final decisions. It is this spirit of generosity and helpfulness that is the hallmark of our profession. Again, we thank you for your work.

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Original Contributions

The Relationship of Complement-Mediated Microvasculopathy to the Histologic Features and Clinical Duration of Disease in Dermatomyositis

John T. Kissel, MD; Richard K. Halterman; Kottil W. Rammohan, MD; Jerry R. Mendell, MD

• Accumulating evidence indicates that a complement-mediated microvasculopathy may play a pathogenic role in dermatomyositis. In a previous study, we demonstrated neoantigens of the C5b-9 complement membrane attack complex in the muscle microvasculature of childhood and adult cases of dermatomyositis. To further characterize the relationship between the vascular complement deposits and histologic changes, quantitative histopathologic analyses were performed on 39 dermatomyositis biopsy specimens (26 adult, 13 children). There was a significant correlation between the percentage of fascicles with fibers having focal myofibrillar loss, a change seen early in the evolution of ischemic muscle fiber damage, and the percentage of fascicles having capillary deposits of membrane attack complex. Conversely, in biopsy specimens with a higher percentage of fascicles with perifascicular atrophy, membrane attack complex deposits were significantly less common. A fascicle-by-fascicle analysis supported these observations. Patients whose biopsy specimens were negative for microvascular membrane attack complex had clinical weakness for a significantly longer time than those patients with vascular complement deposits. These data support the hypothesis that the complement-mediated vasculopathy is a primary immunopathogenic event in the evolution of muscle lesions in dermatomyositis.

(*Arch Neurol.* 1991;48:26-30)

A large number of studies has indicated that different immunopathogenic mechanisms distinguish childhood and adult dermatomyositis from the other idiopathic inflammatory myopathies.[1-11] Most evidence suggests that polymyositis and inclusion body myositis result primarily from direct cellular-mediated cytotoxic mechanisms,[1-5] while the muscle damage in dermatomyositis results from a complement-mediated microvasculopathy.[6-11] In a previous study, we demonstrated the presence of complement C5b-9 membrane attack complex in the intramuscular microvasculature of a significant proportion of dermatomyositis biopsy specimens.[11] These microvascular deposits of membrane attack complex appeared to be most prominent in zones of muscle with features of recent ischemic damage, including muscle fibers with punched-out or rarefied areas of myofibrils, pale-staining necrotic fibers with loss of the intermyofibrillar network, and wedge-shaped regions of contiguous muscle fiber necrosis characteristic of infarction.[3,9,12-15] In other areas of the biopsy specimens, particularly those with prominent perifascicular atrophy, a pathognomonic change of dermatomyositis, microvascular deposits of C5b-9 were scanty. Observations by other investigators demonstrating a loss of capillaries in the perifascicular area[3,7,9] suggested that complement-induced lysis might account for the decreased numbers of capillaries. Collectively, these observations led to the hypothesis that the earliest pathologic event in dermatomyositis is complement activation in the microvasculature followed by ischemic muscle fiber damage, leaving behind residual changes, including perifascicular atrophy and capillary loss.

See also p 21.

The study presented here was designed to test this hypothesis. Detailed quantitative histopathologic analyses were performed on muscle biopsy specimens from 39 patients with dermatomyositis to determine if the vascular C5b-9 deposits were related to the histologic changes observed in dermatomyositis of adults and children. In addition, membrane attack complex deposition in the microvasculature was compared with the duration of clinical disease for each patient.

METHODS

Biopsy Material

Limb muscle biopsy specimens obtained for diagnostic purposes from 39 consecutive cases of dermatomyositis (26 adults, 13 children) were studied. The biopsy specimens were stored at −70°C. Cases fulfilled the criteria of Bohan and Peter[16] for "definite" dermatomyositis, and patients with features of other connective tissue disorders ("overlap" syndromes) were excluded. All patients underwent biopsy prior to institution of immunosuppressive therapy. The biopsy specimens were stained with a battery of histochemical stains, as previously described.[17]

Quantitative Histopathology

Serial 4- to 6-μm cross-sections from each case were stained with modified trichrome and hematoxylin-eosin, and for membrane attack complex. Immunostaining for membrane attack complex employed a rabbit polyclonal antiserum to neoantigens of human C5b-9 and a standard indirect immunoperoxidase method previously reported.[11] For each case, the pattern of fascicles was outlined with the aid of a drawing tube attached to a microscope (Leitz Laborlux) (Fig 1). The fascicles in this outline were then numbered and sequentially examined for the following histologic changes:

1. Fibers with focal myofibrillar loss had "punched-out" or focal pale-staining areas that were usually central or paracentral in location. These fibers did not immunostain for membrane attack complex.
2. Necrotic fibers were pale staining on modified trichrome stain with positive immunostaining for neoantigens of membrane attack complex.[11,18]
3. Regenerating fibers were small with large, pale nuclei, and a basophilic appearance on hematoxylin-eosin staining.
4. Perivascular inflammation consisted of at least 10 mononuclear cells surrounding vessels greater than 30 μm in diameter in the perimysial or epimysial connective tissue.
5. Endomysial inflammation consisted of at least five inflammatory cells in the endomysium surrounding or focally invading muscle fibers.
6. Perifascicular atrophy was defined as a row of contiguous small fibers on at least two sides of the outermost layer of the fascicle adjacent to the perimysium. These fibers often, but not invariably, appeared to be regenerating according to the criteria outlined above.
7. Increased endomysial connective tissue was considered present in an individual fascicle if muscle fibers were consistently separated by at least 5 μm of connective tissue. This figure was chosen after review of the endomysial thickness surrounding 2000 individual normal muscle fibers.
8. Microvascular deposits of membrane attack complex consisted of immunoreactivity confined to the walls of endomysial capillaries.[11]

All histologic determinations were made by two investigators without knowledge of clinical information. Hematoxylin-eosin and trichrome stains were examined and quantitated independently of observations

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on membrane attack complex immunostaining.

Clinical Data

Sufficient clinical information was available on 36 of 39 patients (23 adults, 13 children) to determine the duration of muscle weakness, pain, and fatigue at the time of biopsy.

Statistical Methods

Because the data were not normally distributed, nonparametric statistical methods were employed.[19] Data analyses were performed for all cases together (both childhood and adult), and independently for the adult and childhood groups to explore the possibility that adult and childhood cases behaved differently.

Quantitative Histopathology.—The histologic data were analyzed in two ways to determine if there was a correlation between vascular membrane attack complex deposition and any of the histologic variables examined. In the first analysis, the number of fascicles with each histologic change (eg, perifascicular atrophy, perivascular inflammation) was expressed as a percentage of the total number of fascicles examined for each patient group. These values were then compared with the percentage of all fascicles in each group with capillary membrane attack complex deposits using Kendall's tau correlation.[19]

In the second analysis, the numbers of fascicles with each histologic change *and* capillary membrane attack complex deposits were expressed as a percentage of all fascicles with that particular change (eg, fascicles with perifascicular atrophy and membrane attack complex deposits/total fascicles with perifascicular atrophy × 100%). Standard errors were calculated for each histologic variable and 95% confidence intervals were determined. A significant difference between the percentages for each variable at the $P < .05$ level was confirmed if the confidence intervals did not overlap.[19,20]

Clinical Duration Data.—The duration of clinical disease for each patient was expressed in weeks. The two-sample Wilcoxon rank sum test was then used to compare the durations between patients with and without microvascular membrane attack complex on biopsy for the three patient groups.[19,20]

RESULTS

Histologic Data

An average of eight fascicles was studied for each biopsy specimen (mean 7.8 ± 2.5; range, 4 to 15). Table 1 gives the total number of fascicles and the number and percentage of fascicles with each histologic change for the patient groups. Ten of 13 children and 11 of 26 adults had microvascular deposits of membrane attack complex in at least one fascicle of the biopsy specimen. As shown in Table 2, there was a significant correlation for all the cases between the percentage of fascicles having fibers with areas of focal myofibrillar loss and the percentage of fascicles having capillary deposits of membrane attack complex (correlation coefficient .569, $P = .00001$). This comparison was also significant for adult and childhood cases that were analyzed separately. In biopsy specimens with a higher percentage of fascicles demonstrating perifascicular atrophy, capillary deposits of membrane attack complex were significantly less frequent (correlation coefficient −.492, $P = .0002$). When the groups were analyzed separately, this inverse correlation was definitely significant for the adult cases ($P = .003$), but only approached significance for the childhood cases ($P = .056$). The difference in the childhood and adult cases reflects the higher frequency of deposits of membrane attack complex (10 of 13) in the younger patients, particularly at sites independent of areas of perifascicular atrophy. This point is illustrated in the fascicle-by-fascicle analysis (see below) that demonstrated that deposits of membrane attack complex were rare in fascicles with well-developed perifascicular atrophy in the childhood cases.

There was also a significant positive correlation between necrotic fibers in fascicles and the presence of microvascular membrane attack complex for

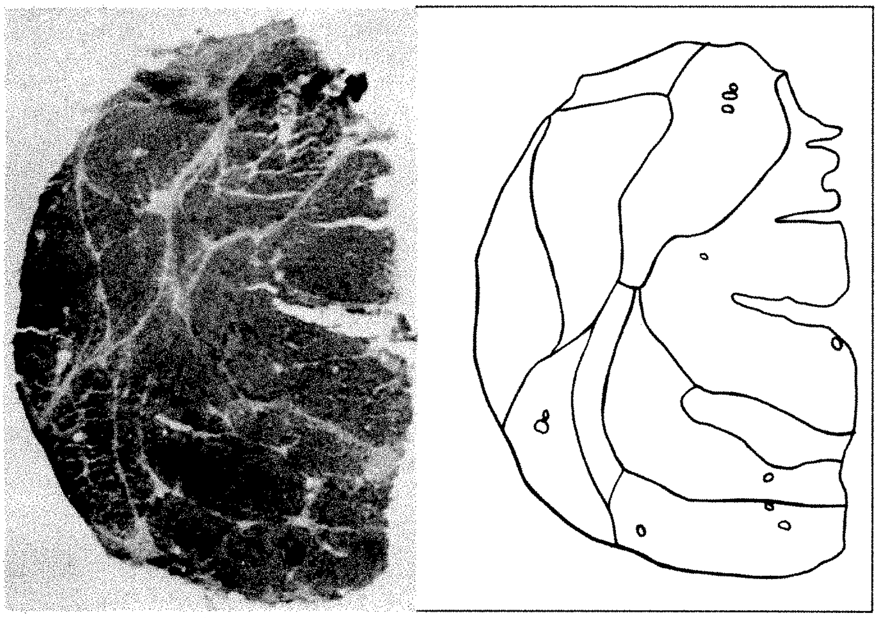


Fig 1.—Representative low-power view of a typical trichrome-stained adult dermatomyositis biopsy specimen (left) and the drawing tube representation of the fascicle pattern (right) used for the quantitative histopathology studies (×20).

Table 1.—Primary Data for Each Histologic Variable by Patient Group*

Group	No.	Fascicles	PFA, No. (%)	FML, No. (%)	NEC, No. (%)	REG, No. (%)	PVI, No. (%)	ENI, No. (%)	ICT, No. (%)
Children	**13**	**102**	**36** (35.2)	**33** (32.4)	**61** (59.8)	**62** (60.8)	**21** (20.6)	**10** (9.8)	**13** (12.7)
MAC +	10	73	8 (10.9)	31 (42.5)	41 (56.2)	34 (46.6)	13 (17.8)	4 (5.5)	0 (0.0)
MAC −	3	29	28 (96.6)	2 (6.9)	20 (69.0)	28 (96.6)	8 (27.6)	6 (20.7)	13 (44.8)
Adults	**26**	**203**	**64** (31.5)	**51** (25.1)	**124** (61.1)	**108** (53.2)	**39** (19.2)	**33** (16.2)	**20** (76.9)
MAC +	11	90	4 (4.4)	41 (45.5)	69 (76.7)	52 (57.8)	12 (13.3)	9 (10.0)	11 (12.2)
MAC −	15	113	60 (53.1)	10 (8.8)	55 (48.7)	56 (49.6)	27 (23.9)	24 (21.2)	9 (8.0)
All	**39**	**305**	**100** (32.8)	**84** (27.5)	**185** (60.6)	**170** (55.7)	**60** (19.7)	**43** (14.1)	**33** (10.8)
MAC +	21	163	12 (7.4)	72 (44.2)	110 (67.5)	86 (52.8)	25 (15.3)	13 (8.0)	11 (6.7)
MAC −	18	142	88 (62.0)	12 (8.4)	75 (52.8)	84 (59.2)	35 (24.6)	30 (21.1)	22 (15.5)

*MAC indicates membrane attack complex; PFA, perifascicular atrophy; FML, focal myofibrillar loss; NEC, necrotic fibers; REG, regenerating fibers; PVI, perivascular inflammation; ENI, endomysial inflammation; and ICT, increased connective tissue.

the adult population and for all patients analyzed together (Table 2). None of the other histologic variables were related to complement deposition except for increased connective tissue, which showed an inverse relationship ($P = .011$) in the childhood cases.

Data specifically correlating capillary deposits of membrane attack complex and regional histologic changes are presented in Fig 2. Fascicles with fibers showing focal myofibrillar loss (Figs 3 and 4) were significantly more likely to have microvascular complement deposits than were fascicles with perifascicular atrophy (Fig 5) or perivascular inflammation. This observation was also valid for both childhood and adult cases that were analyzed separately. The degree of capillary and myofiber involvement differed significantly between fascicles. In some areas, well-defined circumferential capillary immunostaining was seen, often in association with only a few fibers with focal myofibrillar loss (Fig 3). In other fascicles with more advanced involvement, the capillary immunostaining assumed a more punctate appearance due to underlying capillary necrosis. In these fascicles, multiple fibers with focal myofibrillar loss were usually encountered (Fig 4).

Duration Data

The mean duration of disease and P values for the patient groups are presented in Table 3. As shown, patients whose biopsy specimens were negative for capillary membrane attack complex had had clinical disease significantly longer ($P = .0006$) than those patients with membrane attack complex in the microvasculature. This was particularly true for the adult patients who were considered separately. In the childhood cases, the duration of disease in relation to membrane attack complex deposits fell just below statistical significance ($P = .06$). This might be accounted for by an earlier presentation of the childhood cases or a greater likelihood of membrane attack complex deposits throughout the duration of the illness, representing more homogeneity in the pathogenesis of childhood cases compared with adult cases.

COMMENT

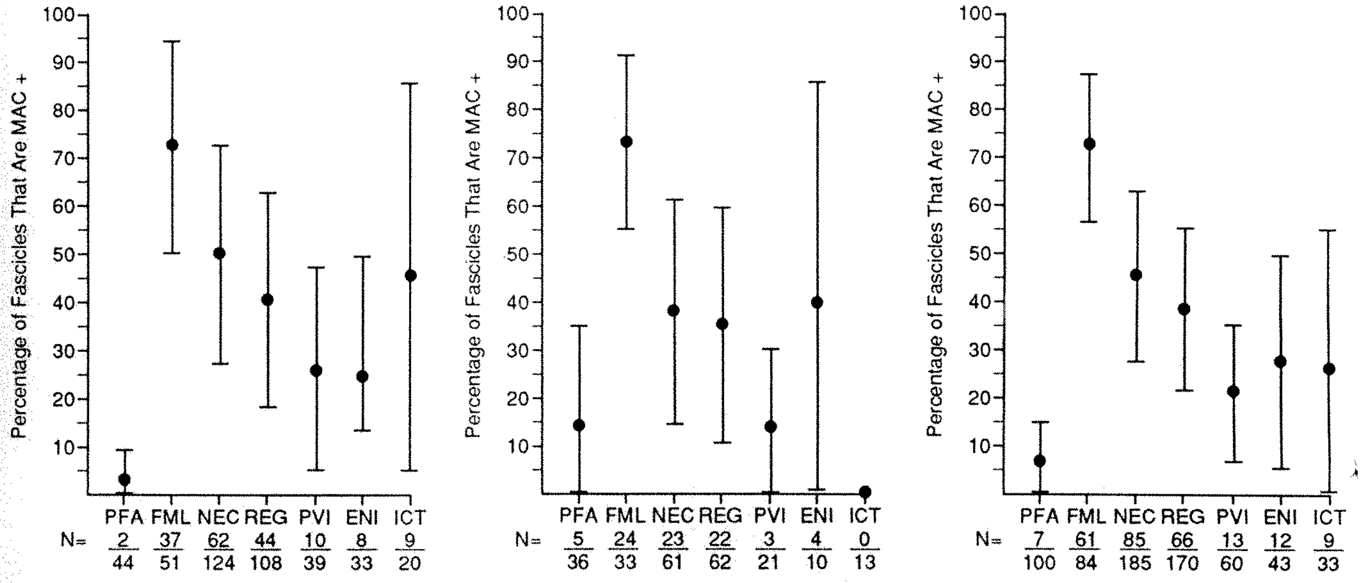
We hypothesized that, in dermatomyositis, complement deposition in the microvasculature is the earliest immunopathologic event that leads to capillary damage and muscle ischemia.[11] To test this hypothesis, muscle fiber histologic changes were analyzed in relation to deposits of membrane attack complex in the endomysial capillaries. Although microvasculature complement deposits are frequently seen in larger vessels in the perimysial connective tissue in both childhood and adult cases,[11] these vessels may be supplying blood to regions of muscle out of the plane of section, and, therefore, were not analyzed in this study. An additional methodological consideration is that for this study the histo-

Table 2.—Comparison of Fascicle Histologic Changes With Presence of Vascular Deposits of Membrane Attack Complex*

	PFA	FML	NEC	REG	PVI	ENI	ICT
Children (n = 13)							
Correlation coefficient	−.449	.510	.194	−.084	−.377	−.270	−.615
P value	.056	.021	NS	NS	NS	NS	.011
Adults (n = 26)							
Correlation coefficient	−.492	.596	.399	.078	−.130	−.076	.174
P value	.003	.0003	.012	NS	NS	NS	NS
All (n = 39)							
Correlation coefficient	−.492	.569	.345	.016	−.202	−.154	−.079
P value	.0002	.00001	.0052	NS	NS	NS	NS

*For each comparison, the total number of fascicles in each patient group with a given histologic change was expressed as a percentage of all fascicles examined in that group. This was then compared with the percentage of fascicles with capillary membrane attack complex in each group. The numbers represent Kendall's tau correlation coefficient and corresponding *P* value for each comparison. Abbreviations are the same as those used in Table 1. NS indicates not significant.

Fig 2.—Comparison of the percentages of fascicles with positive vascular membrane attack complex immunostaining for the adult cases (left), childhood cases (center), and all cases analyzed together (right). The percentages on the ordinate represent the numbers of fascicles with each histologic change *and* capillary membrane attack complex deposits divided by the total number of fascicles with each histologic change. Bars represent 95% confidence intervals for each change. Lack of overlap between the confidence intervals indicates a significant difference between the proportions at the $P < .05$ level. See text for details. Abbreviations for histologic changes are the same as in Table 1.



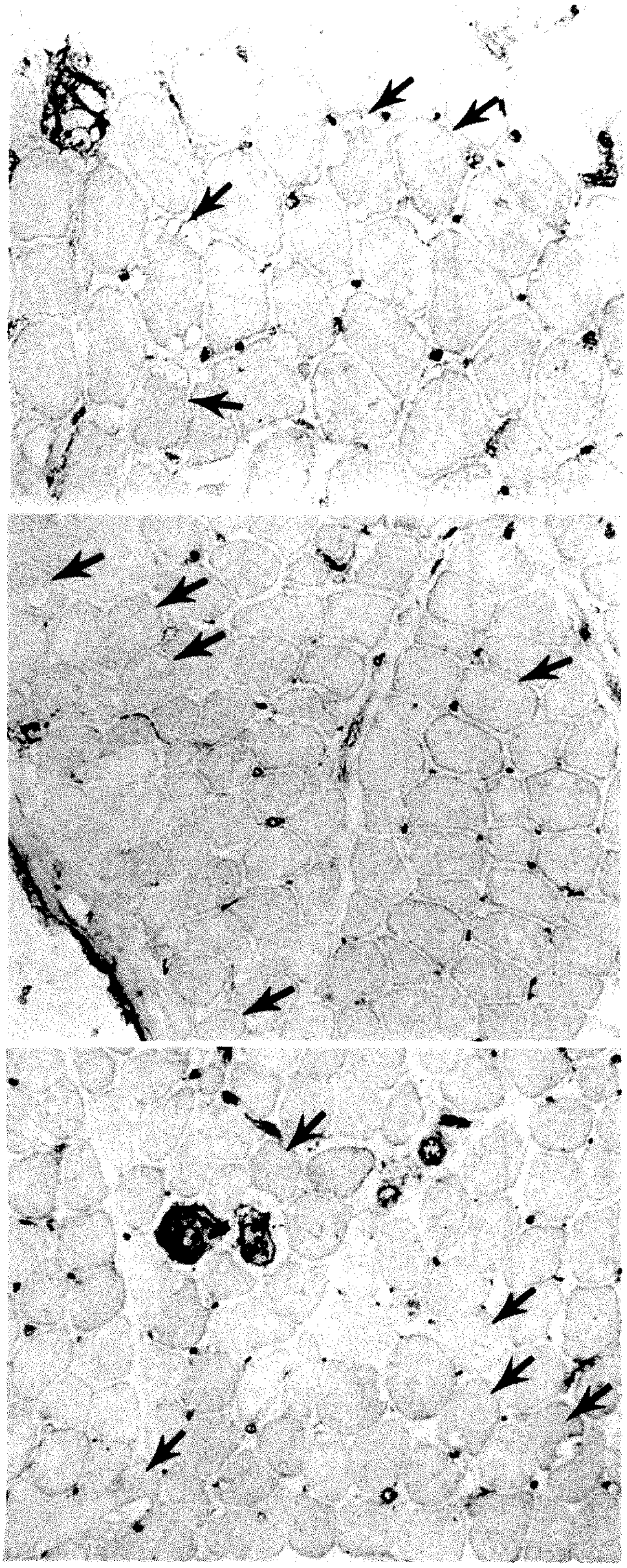


Fig 3.—Three representative areas from a childhood dermatomyositis biopsy specimen immunostained for membrane attack complex. Well-defined microvascular deposits are seen in fascicles with fibers having focal areas of myofibrillar loss (arrows). In top and bottom parts, necrotic muscle fibers also immunostain for membrane attack complex (top, ×260; center and bottom, ×200).

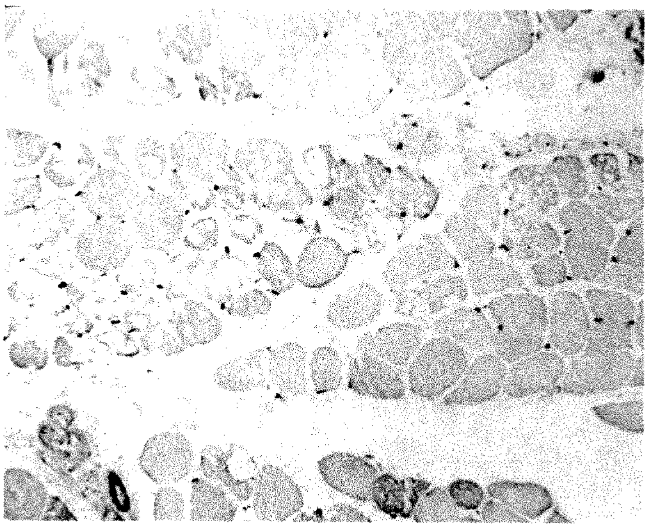


Fig 4.—Adult dermatomyositis biopsy specimen immunostained for complement membrane attack complex. In fascicles with multiple fibers having focal myofibrillar loss, intense punctate deposits are seen in the capillaries (×125).

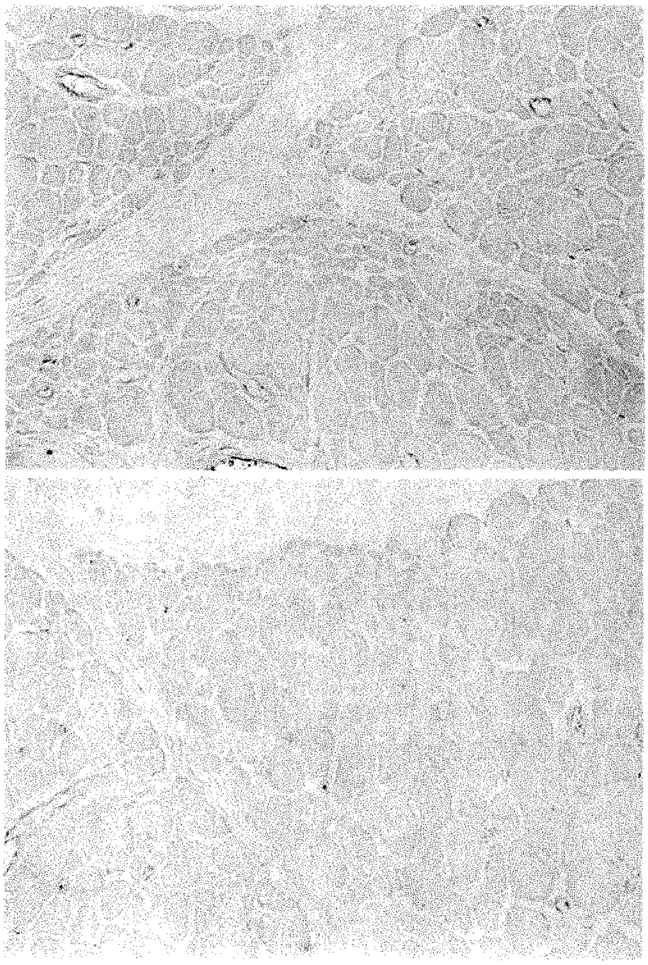


Fig 5.—Two areas (top and bottom) from an adult dermatomyositis biopsy specimen immunostained for membrane attack complex. The fascicles with prominent perifascicular atrophy have no microvascular deposits of membrane attack complex anywhere in the fascicle (×125).

Table 3.—Comparison of Disease Duration in Weeks for Patient Groups*

Group	No.	Mean Duration†	P Value‡
Children	13		
MAC +	10	6.7 ± 1.3	.063
MAC −	3	18.0 ± 6.0	
Adults	23		
MAC +	10	9.4 ± 2.7	.0112
MAC −	13	29.5 ± 4.9	
All	36		
MAC +	20	8.0 ± 1.4	.0006
MAC −	16	27.4 ± 4.3	

*MAC indicates membrane attack complex.
†Duration is expressed in weeks ± SEM.
‡P values were determined using the Wilcoxon rank-sums test.

logic changes in relation to complement deposition were analyzed separately for the biopsy specimen as a whole, as well as in relation to each individual fascicle. The latter analysis provided a satisfactory means to correlate capillary membrane attack complex deposits directly with contiguous histologic changes. This type of analysis is important in a disease such as dermatomyositis, where areas of a biopsy specimen may have markedly different histologic changes reflecting insults occurring at separate times in the evolution of the disease.

Our analysis revealed that membrane attack complex deposits in the microvasculature correlated significantly with the presence of fibers having focal areas of myofibrillar loss, a histologic change seen early in the evolution of ischemic muscle fiber damage.[9,12,13,15] This association was true in a fascicle-by-fascicle analysis, as well as for the entire specimen. Conversely, in fascicles with perifascicular atrophy, microvascular complement deposits were significantly less common, both in the perifascicular areas and in the more central regions of the fascicle. Our interpretation of these findings is that the association of microvascular deposits of membrane attack complex with early histologic changes of muscle fiber ischemia suggests a primary role for the complement system in the immunopathogenesis of the disease. Further support for this concept was provided in our study by comparing disease duration with the muscle biopsy findings. Microvascular complement deposits were significantly more common if the time interval between the onset of symptoms and muscle biopsy specimen examination was shorter. Independent histologic observations support this point of view. Recent studies by DeVisser et al[21] and Emslie-Smith and Engel[22] demonstrated that capillary deposits of membrane attack complex and reduced capillary density actually preceded muscle fiber damage in unaffected or minimally affected regions of muscle in adult patients with dermatomyositis.

Although our findings provide strong evidence that complement deposits occur early in the disease process, the results also raise the question of whether humoral immune mechanisms, specifically the complement system, represent a singular pathogenic mechanism in this disease. The findings of other investigators, especially in adult cases, support a possible transition or collaboration with other immune mechanisms. For example, in studies by Arahata and Engel,[4] the mononuclear cell subsets in dermatomyositis demonstrated a significant percentage of CD8$^+$/cytotoxic T cells and macrophages in addition to B cells and CD4$^+$/helper T cells, raising the possibility of cellular-mediated muscle fiber damage. These findings are of interest in light of studies demonstrating class I major histocompatibility complex gene products on muscle fibers from cases of dermatomyositis.[23,24] Such expression of class I antigens would be a necessary prerequisite for direct cytotoxic T-cell damage in dermatomyositis. These findings could be relevant in some cases of dermatomyositis where a clinically prolonged and more severe course is associated with marked perifascicular atrophy and absence of microvascular complement deposits on biopsy.

In summary, the clinical and histologic data presented here strongly support the concept that complement activation occurs as a primary immunopathogenic event in the evolution of muscle lesions in dermatomyositis. The variability in complement deposits in the muscle tissue of patients with dermatomyositis appears to depend on the area of muscle sampled,[11,21,22] as well as the time of muscle biopsy in relation to the evolution of the disease process. The data also suggest that complement may not be the only pathogenically significant immune mechanism throughout the entire course of the disease. Further understanding and definition of these immune mechanisms in dermatomyositis will be important in devising better treatment strategies for the future.

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References

1. Mastaglia FL, Ojeda VJ. Inflammatory myopathies. *Ann Neurol.* 1985;17:215-227, 317-323.
2. Whitaker JN. Inflammatory myopathy: a review of etiologic and pathogenetic factors. *Muscle Nerve.* 1982;5:573-592.
3. Carpenter S, Karpati G. The major inflammatory myopathies of unknown cause. *Pathol Annu.* 1981;16:205-237.
4. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies, I: quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T-cells. *Ann Neurol.* 1984;16:193-208.
5. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies, IV: cell-mediated cytotoxicity and muscle fiber necrosis. *Ann Neurol.* 1988;23:168-173.
6. Banker BQ, Victor M. Dermatomyositis (systemic angiopathy) of childhood. *Medicine (Baltimore).* 1966;45:261-289.
7. Jerusalem F, Rakusa M, Engel AG, MacDonald RD. Morphometric analysis of skeletal muscle capillary ultrastructure in inflammatory myopathies. *J Neurol Sci.* 1974;23:391-402.
8. Banker BQ. Dermatomyositis of childhood: ultrastructural alterations of muscle and intramuscular blood vessels. *J Neuropathol Exp Neurol.* 1975;34:56-75.
9. Carpenter S, Karpati G, Rothman S, Watters G. The childhood type of dermatomyositis. *Neurology.* 1976;26:952-962.
10. Whitaker JN, Engel WK. Vascular deposits of immunoglobulin and complement in idiopathic inflammatory myopathy. *N Engl J Med.* 1972;286:333-338.
11. Kissel JT, Mendell JR, Rammohan KW. Microvascular deposition of complement membrane attack complex in dermatomyositis. *N Engl J Med.* 1986;314:329-334.
12. Munsat TL, Hudgson P, Johnson MA. Experimental serotonin myopathy. *Neurology.* 1977;27:772-782.
13. Karpati G, Carpenter S, Melmed C, Eisen AA. Experimental ischemic myopathy. *J Neurol Sci.* 1974;23:129-161.
14. Mendell JR. Experimental myopathies: a review of experimental models and their relationship to human neuromuscular diseases. In: Vinken PJ, Bruyn GE, eds. *Handbook of Clinical Neurology.* Amsterdam, the Netherlands: North Holland; 1979;40:133-182.
15. Carpenter S, Karpati G. *Pathology of Skeletal Muscle.* New York, NY: Churchill Livingstone Inc; 1984:524-535, 592-596.
16. Bohan A, Peter JP. Polymyositis and dermatomyositis. *N Engl J Med.* 1975;292:344-347, 403-407.
17. Dubowitz V, Brooke MH. *Muscle Biopsy: A Modern Approach.* Philadelphia, Pa: WB Saunders Co; 1973:20-33.
18. Engel AG, Beisecker G. Complement activation in muscle fiber necrosis: demonstration of the membrane attack complex of complement in necrotic fibers. *Ann Neurol.* 1982;12:289-296.
19. Hollander M, Wolfe D. *Nonparametrical Statistical Analysis.* New York, NY: John Wiley & Sons Inc; 1973.
20. Cochran WG. *Sampling Techniques.* New York, NY: John Wiley & Sons Inc; 1977:155.
21. DeVisser M, Emslie-Smith AM, Engel AG. Early ultrastructural alterations in adult dermatomyositis. *J Neurol Sci.* 1989;94:181-192.
22. Emslie-Smith AM, Engel AG. Microvascular changes in early and advanced dermatomyositis: a quantitative study. *Ann Neurol.* 1990;27:343-356.
23. Karpati G, Pouliot Y, Carpenter S. Expression of immunoreactive major histocompatibility complex products in human skeletal muscles. *Ann Neurol.* 1988;23:64-72.
24. Emslie-Smith AM, Arahata K, Engel AG. Major histocompatibility antigen expression, immunolocalization of interferon subtypes, and T-cell-mediated cytotoxicity in myopathies. *Hum Pathol.* 1989;20:224-231.

Early Combination of Selegiline and Low-Dose Levodopa as Initial Symptomatic Therapy in Parkinson's Disease

Experience in 26 Patients Receiving Combined Therapy for 26 Months

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• Thirty-eight patients newly diagnosed as having Parkinson's disease (mean age, 57.3 years; mean Parkinson's disease duration, 2.7 years) in the earlier phase of the disease (mean Hoehn/Yahr stage, 2; mean motor scores, 11.4) were given selegiline (Deprenyl), 10 mg daily, and maintained on this drug alone until significant clinical worsening warranted the addition of low-dose levodopa (Sinemet, 25/100 three to four doses per day). Five of these patients were not yet receiving additional levodopa despite some worsening of motor scores. Of the 33 patients now taking combined therapy, seven have been followed up for 6 months or less. Twenty-four (92%) of the 26 patients taking combined therapy for a mean of 26 months (8.5 to 99 months) who have had Parkinson's disease for 6 years showed a dramatic improvement in their parkinsonism shortly after the addition of levodopa, with significant decreases in their rated motor scores, such improvement being maintained at their latest neurologic evaluation. Eighteen (75%) of these 24 patients responded to the combined selegiline/levodopa therapy with degrees of improvement equal to or greater than 50%, compared with their motor status at the start of combined therapy just before the addition of levodopa. This degree of "reversal" of parkinsonism on addition of levodopa (mean carbidopa/levodopa dose, 98/389 mg) was *not* observed in any of these same patients receiving selegiline alone for an average of 13.8 months. Four patients taking combined therapy developed mild, transient, abnormal involuntary movements, and end-of-dose pattern of response after more than 2 years of combined therapy (24.75 and 33.5 months, respectively). Our results on combined selegiline/levodopa therapy reemphasize the continuing dominant role of levodopa as the primary drug for the symptomatic treatment of Parkinson's disease. A possible synergistic role of selegiline with levodopa in the early cases is suggested by the sustained therapeutic effectiveness of even low doses of the latter for a period of 26 months, with a delay in the appearance of relatively minor side effects developing only after more than 2 years of combined therapy. At an average disease duration of 6 years, no patient has had a major functional disability. A concurrently studied control group of patients treated with low-dose levodopa alone, or one treated with a combination of low-dose levodopa and a dopamine agonist like bromocriptine or pergolide, may have clarified further the role of selegiline, but such control subjects were not available to us at this time. We suggest the early combination of a selective monoamine oxidase type B inhibitor like selegiline, and the original dopamine replacement drug, levodopa (as low-dose Sinemet), as initial symptomatic therapy in newly diagnosed cases of Parkinson's disease.

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Selegiline (L-Deprenyl), an amphetamine-derived, potent, irreversible inhibitor of the enzyme monoamine oxidase type B, has been under investigation since 1975 as an agent that may arrest or slow the natural progression of Parkinson's disease (PD).[1] Although originally designed as an antidepressant, the drug's pharmacologic features[2,3] have led to its use as an adjunctive agent to levodopa, as recently reviewed.[4,5] Briefly, the current underlying rationale for its use is based on two kinds of observations: (1) monoamine oxidase inhibitors, including selegiline, prevent the biological (toxic) effect of 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) on dopamine neurons in experimental animals[6-8]; (2) during catabolism of dopamine by monoamine oxidase, a potential cellular oxidant, hydrogen peroxide, is formed, and selegiline appears to suppress such an oxidative stress associated with increased dopamine turnover in animal models.[9,10] Increased dopamine turnover that inevitably occurs in PD may be viewed as a potential source of an oxidant stress. This protective role of selegiline in experimental systems would be most relevant if indeed idiopathic PD in man is caused by a toxin (endogenous or exogenous), for which no definitive evidence, as yet, exists.

We recently presented our clinical experience with selegiline on 22 de novo patients with early PD,[11] and as an adjunct to long-term conventional levodopa (Sinemet) therapy in 200 patients with advanced PD.[5] Selegiline by itself does not halt the clinical progression even in early PD,[11] but may apparently delay the onset of functional disability compared with the course of early, otherwise *untreated*, control subjects.[12,13] When given much later in the course of the disease as an adjunct to long-term levodopa therapy, selegiline mildly improved the parkinsonian state for a limited time in a selected group of patients experiencing an end-of-dose pattern of response to levodopa.[5]

In following the course of our de novo patients taking selegiline alone,[11] we were impressed with the observation that almost immediately (within weeks) after the addition of a starting minimal dose of levodopa, the worsening parkinsonism dramatically improved, such improvement being maintained. Additionally, we know from our extensive experience with levodopa since 1968, that an optimal levodopa dose is generally reached within the first year of treatment. This article focuses on our experience with the early combination of selegiline and low-dose levodopa as initial symptomatic therapy in early PD.

PATIENTS AND METHODS

Patients registered at the Mount Sinai Parkinson's Center (New York, NY) with newly diagnosed PD in its early phase, and who had not had previous selegiline or levodopa therapy, agreed to participate in this study, and signed informed consent forms approved by Mount Sinai's institutional review board on human studies. To date, 38 patients have chosen to be involved. All had a complete neurologic evaluation

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just before entering the study, and their parkinsonian state was rated by two neurologists at regular intervals using Mount Sinai Center's functional staging of disease severity (stages I through V) and rated motor disability scores (25 items, rated 0 to 4). Twenty-one of these patients were in the original group of 22 de novo patients tried on selegiline alone, whose treatment results we recently presented.[11] These patients received selegiline, 5 mg twice a day, and no other therapeutic agents, until such time as their condition showed functionally significant progression, determined by more than 25% deterioration in their parkinsonian-rated examination and/or advancement to a more severe functional stage of the disease. At such time, the patient was offered the opportunity of having levodopa (Sinemet) added, which was usually begun at a minimum dosage (25/100, two to three doses per day) and titrated to achieve optimal antiparkinsonian effect. Nine other de novo patients were similarly treated with selegiline and given additional levodopa when worsening functional deficits when receiving selegiline alone warranted such addition. In an additional eight de novo patients treatment was started almost simultaneously with both selegiline and levodopa within days of one drug and the other, without waiting for any further change in the course of the disease while receiving one drug alone.

At the start of the trial, these 38 patients had a mean age of 57.3 years, mean PD duration of 2.7 years, mean Hoehn/Yahr stage of 2.0, and mean motor scores of 11.4. At their latest neurologic evaluation, five of these patients receiving selegiline alone for an average of 25.6 months, had not yet elected to take additional levodopa, despite some worsening of their motor scores. Seven patients have been given combined selegiline/levodopa therapy for 6 months or less. The remaining 26 patients who have been receiving combined therapy for more than 6 months (mean of 26 months) constitute the subject of this article.

Table 1.—Patients With Idiopathic Parkinson's Disease (PD) Receiving Early Combined Selegiline/Levodopa Therapy for Over 6 Months[*]

Age at PD onset (y)	56.1	(41-75)
PD duration at start of therapy (y)	2.8	(1-8)
PD duration at latest examination on combined therapy (y)	6.0	(3.1-11.25)
Total duration on combined therapy (mo) 16 (62%) >6 to 24 mo 10 (38%) >24 to >60 mo	26.0	(8.5-99.0)
Sinemet dose at latest examination on combined therapy	98 mg carbidopa (50.0-225 mg) 389 mg levodopa (100-900 mg)	
Selegiline maintenance dose on combined therapy	10 mg	. . .

[*] N = 26; 16 men and 10 women.

Table 2.—Patients Taking Early Combined Selegiline/Levodopa Therapy for Over 6 Months[*]

Patient	Stage/Scores at Start of Combined Selegiline/Levodopa Therapy	Stage/Scores at Latest Neurologic Evaluation Over 6 mo From Start of Combined Selegiline/Levodopa Therapy
1	II/25.5	II/10.5
2	II/22.0	I/1.0
3	II/16.0	II/4.5
4	II/15.5	II/14.5
5	II/17.0	I/3.5
6	II/17.5	II/6.0
7	II/15.5	II/3.0
8	III/19.0	II/3.0
9	II/15.0	II/6.0
10	II/17.0	II/1.5
11	III/27.0	III/39.5
12	III/18.0	III/15.0
13	II/14.0	II/8.5
14	II/13.0	II/2.5
15	II/22.0	II/4.0
19[†]	III/19.0	0/0.5
21[†]	II/8.0	II/7.5
22[†]	III/20.0	II/5.5
24[†]	II/26.0	II/15.0
25[†]	III/14.0	0/0
26[†]	II/18.0	II/8.0
27[†]	II/14.0	II/17.0
28	II/12.0	II/6.5
29	II/17.5	II/4.5
30	II/15.0	I/2.5
31[†]	II/22.0	II/9.0

[*] N = 26 patients.

[†] Patients were started almost simultaneously on selegiline/levodopa therapy.

RESULTS

Table 1 shows the demographics of this patient population. At the start of their combined selegiline/levodopa therapy, just before the addition of levodopa, these 26 patients had been receiving selegiline alone for an average of 13.8 months. At the time of their latest neurologic evaluation, 62% of these patients had been taking combined therapy for 8 to 24 months, and 38% for over 2 to 5 years (average duration of 26 months). At this time, they had had PD for an average of 6 years and were given an average Sinemet dose of 98 mg, carbidopa, and 389 mg of levodopa. The maintenance dose of selegiline, 10 mg a day, was unchanged from that previous to the addition of levodopa.

Table 2 shows the disease stage and parkinsonian motor scores of each of these 26 patients at the start of the combined selegiline/levodopa therapy, and at their latest neurologic evaluation. In the eight patients marked with asterisks treatment was begun almost simultaneously with both drugs. The most striking "reversal" of parkinsonism occurred in two of these patients (patients 19 and 25), with almost normal motor status after over 2½ years (32 months) of receiving combined therapy (on 93.75/375 mg Sinemet), who have had the disease for 7 and 4 years, respectively. Of the 24 patients that did improve by taking combined therapy, the average improvement was 65%. Two patients (patients 11 and 27) with unchanged stages and mildly worsening motor scores (27 vs 39.5 and 14 vs 17) at their latest evaluation 8.25 years and 3.3 years after start of their combined therapy, respectively, were on the 11th and sixth year of their disease, and have had a gradual worsening of scores before and after the start of combined therapy.

Table 3 summarizes the severity of parkinsonism in these 26 patients before any therapy was given; at the start of combined therapy (or just before addition of levodopa after a trial with selegiline alone for an average of 19.8 months in 18 of 26 patients); and, at the latest examination, over 6 months from start of combined ther-

Table 3.—Severity of Parkinsonism in Patients Receiving Early Combined Selegiline/Levodopa Therapy for Over 6 Months*

	Disease Stage		Motor Scores’	
	Total	Average	Total	Average
Before therapy	56	2.2	338	13
At start of combined therapy	58	2.2	460	18
At latest examination >6 mo from start of combined therapy	46	1.8	199	8

*N = 26 patients.

Table 4.—Improvement in Motor Scores of 24 Patients Receiving Combined Selegiline/Levodopa Therapy for Over 6 Months*

No. (%) of Patients	Degrees of Improvement, %
9 (37.5)	80-100
9 (37.5)	50-79
3 (12.5)	20-49
3 (12.5)	0-19

*Seventy-five percent of 24 patients responded on the combined selegiline/levodopa therapy with a degree of improvement equal to or greater than 50%.

Table 5.—Untoward Events Developing During Combined Selegiline/Levodopa Therapy

Event	No. of Patients	Comment
Death (cancer, lung; myocardial infarction)	1	Patient had been taking combined therapy for 8.75 months until death
"Bleeding" peptic ulcer	1	Patient had been taking combined therapy for 47.5 months when selegiline was stopped
End-of-dose deterioration	4	Event was first noted on the 40th, 36th, 34th, and 24th month of combined therapy, respectively
Abnormal involuntary movements	5	Event was first noted on the 36th, 34th, 18th, 16th, and 13th month of combined therapy, respectively

apy. There was a worsening of motor scores greater than 30% (36%) from initial evaluation to the start of combined therapy. A striking improvement of motor scores greater than 50% (57%) was noted at the latest examination over 6 months from start of combined therapy compared with status at the start of combination treatment. This "reversal" of deteriorating motor scores was evident even when comparison was made with the initial pretherapy scores (41% better than pretherapy scores).

Table 4 shows the degrees of improvement in motor scores of 24 of 26 patients who improved by taking combined therapy. Eighteen (75%) of the 24 patients responded with degrees of improvement equal to or greater than 50%. Seven of these patients also had a concurrent shift to at least one functional stage better than at the beginning of combined therapy (Table 2). These degrees of improvement or "reversal" of parkinsonism were *not* observed in any of these same patients receiving selegiline alone for over 1 year. All patients have remained totally functional with no major parkinsonian disability at an average disease duration of 6 years.

Table 5 shows the untoward events that developed during combined therapy. One patient (patient 16) died suddenly of myocardial infarction and a recently discovered lung cancer, 2 months after his latest neurologic evaluation at which time he showed improving motor scores (66% change) after almost 9 months of taking combined therapy. This 70-year-old man was taking selegiline alone for 2 years during which time he continued to deteriorate, almost doubling his motor scores. Reversal of scores occurred within 1 month after addition of levodopa. He returned to work 5 months later. Before he died he was still receiving a maintenance dose of 10 mg of selegiline and 100/400 mg of Sinemet. One patient (patient 12) had been taking selegiline alone for 7 months, and receiving combined selegiline/levodopa for another 47.5 months, when he had a bleeding peptic ulcer and he stopped the selegiline. Now he is only taking Sinemet 200/800 mg daily. Four patients (patients 11, 12, 24, and 27) first developed an end-of-dose "wearing off" pattern of response on the 40th, 36th, 24th, and 34th month, respectively, of combined therapy (mean, 2.8 years after addition of levodopa). Interestingly, the same four patients also first developed abnormal involuntary movements at the 16th, 36th, 13th, and 34th month, respectively, of combined therapy (mean, 2.0 years after addition of levodopa). Sinemet doses at those times were 100/400, 225/900, 125/500, and 75/750 mg daily, respectively (or a mean of 131 mg of carbidopa/637.5 mg of levodopa). The abnormal involuntary movements were focal, localized to small muscle groups of the hand, foot, or face, transitory (seconds), infrequently occurring, and were at no time disabling. One more patient (patient 13) developed one episode of mild, transient "curling up of left foot" at the 18th month after Sinemet was added at a dose of 75/300 mg. There have been no instances of mental confusion, disorientation, hallucinations, behavioral changes, or changes in higher cognitive functions ever occurring in any of these 26 patients during this combined drug trial, which has now lasted for a mean duration of 26 months or 2.2 years (range, 0.7 to 8.3 years; median, 4.5 years).

COMMENT

Our results on combined selegiline/levodopa therapy reemphasize the continuing dominant role of levodopa as the primary drug for symptomatic treatment of PD. It was the addition of initial small doses of levodopa to a deteriorating parkinsonism on selegiline alone for an average of 13.8 months that rapidly and dramatically "reversed" the clinical worsening in most of our patients. Seventy-five percent of the 24 patients who did improve responded with degrees of improvement in their motor scores by as much as, or better than 50%, with a concurrent shift of at least one functional stage in about a third. These results are similar to those of the earliest article by Yahr et al[14] in 1971 on levodopa and MK-486 (α-methyl-dopa hydrazine), where 89% of their 38 patients had better than 50% improvement on the then new combination of levodopa and a peripheral decarboxylase inhibitor. Yahr et al noted that such results obtained within the first weeks of combined treatment were similar to those they had found after 6 to 12 months of treatment with gradually increasingly large doses of levodopa alone. Just as Yahr et al were impressed with the "effective, rapid and efficient means of reversing the parkinsonian state" with levodopa/MK-486 in 1971, we were impressed anew with the relatively dramatic reversal of parkinsonism with low doses of levodopa-carbidopa when added to a previous regimen of selegiline alone. This was particularly impressive in two of eight patients in whom treatment with both drugs was started almost simultaneously, with rapid reversal to almost normal motor status, maintained after over 2½ years on combined therapy. The quality of the therapeutic response was not related to the age of onset, severity, or duration of PD at the start of selegiline/levodopa therapy. A possible synergistic role of selegiline with levodopa in these early cases of PD is suggested by the sustained therapeutic effectiveness of even low doses of the latter for an average of 26 months, with a delay in the appearance of relatively minor side-effects that developed only after over 2 years of combined therapy. At an average PD duration of 6 years (range, 3 to 11 years), no patient has had a major functional disability. While these patients have now been followed up for over 2 years, it remains too early to draw any definitive conclusions regarding the specific role of either drug in this combination. A concurrently studied, appropriately matched control group of low-dose levodopa alone or in combination with a dopamine agonist such as bromocriptine or pergolide was not available to us at this time. Three articles in the recent literature address the issue of bromocriptine compared with, or in early combination with, levodopa, and present some data that may be historically relevant for our study. Libman et al[15] assessed the short-term efficacy and tolerance of bromocriptine (Parlodel) and levodopa-carbidopa in a double-blind parallel group design multicenter study of 49 de novo patients followed up for 3 months. The majority of their patients (21 in the bromocriptine group and 17 in the levodopa-carbidopa group) were in stage II or III of their disease at the beginning of the study, comparable with our own study group. At the end of 3 months, 42% of the patients in the bromocriptine group and 32% in the levodopa-carbidopa group had improved in their parkinsonian status by at least one functional stage. The total mean neurologic assessment scores had improved by 62% in the bromocriptine group and by 55% in the levodopa-carbidopa group. Comparison between the groups did not show any significant difference for both neurologic and disability assessments. The mean daily dose for responders at the end of 3 months was 22.5 mg of bromocriptine and 250 mg of levodopa. The most significant side effect observed was transient nausea occurring in six of 24 patients receiving bromocriptine and in three of 25 patients receiving levodopa-carbidopa. Rinne[16,17] described his experience with the early combination of bromocriptine and levodopa in patients with PD. Compared with levodopa alone, treatment with bromocriptine alone for 3 years, and then for 5 years, resulted in fewer fluctuations in disability and peak-dose dyskinesias, but also less improvement in parkinsonian disability. After 3 years of combined bromocriptine/levodopa treatment of 28 patients,[16] the mean daily doses of bromocriptine (16.6 ± 1.9 mg) and levodopa (660 ± 35 mg) were significantly lower than in patients treated with either drug alone (bromocriptine, 28.0 ± 4.3 mg in 21 patients; levodopa, 798 ± 12 mg in 217 patients). Three years of combined treatment resulted in significant improvement of parkinsonian disability equal to that achieved with levodopa alone (39% ± 3% vs 37.0% ± 1%), and significantly better than with bromocriptine alone (15% ± 3%). On a 3-year follow-up of patients treated with levodopa alone, there were fluctuations in motor disability in 51 (24%) of 217 patients; there were significantly fewer ($P < .05$) fluctuations in patients taking combined therapy. At 5 years of combined bromocriptine/levodopa therapy in 25 patients,[17] improvement of parkinsonism was equal to that observed in 196 patients receiving levodopa alone (23%). Rinne[17] concluded that as primary treatment, bromocriptine alone is not a useful antiparkinsonian agent, but that the early combination of low-dose bromocriptine and levodopa-carbidopa can result in a therapeutic response equal to that of levodopa alone, but with few end-of-dose fluctuations and peak-dose dyskinesias.

Our own initial results with the early combination of selegiline/levodopa compare favorably with the above historic data in the literature. We can only suggest that the early combination of a selective monoamine oxidase type B inhibitor, like selegiline, with its intriguing, possibly protective role in dopaminergic cell death due to a toxic cause,[18,19] and the original dopamine replacement drug, levodopa, both given at the earliest clinical expression of the disease process (when at best, only 20% of dopaminergic neurons may still be functionally intact), seems a most reasonable approach as initial symptomatic therapy in de novo patients with PD.

References

1. Birkmayer W, Riederer P, Youdim MBH, Linauer W. The potentiation of the antiakinetic effect after L-dopa treatment by an inhibitor of MAO-B, deprenyl. *J Neural Transm.* 1975;36:303-326.
2. Knoll J, Magyar K. Some puzzling effects of monoamine oxidase inhibitors. *Adv Biochem Psychopharmacol.* 1972;5:393-408.
3. Knoll J. Extension of life span of rats by long-term (-)deprenyl treatment. *Mt Sinai J Med.* 1988;55:67-74.
4. Riederer P, Przuntek H. MAO-B inhibitor selegiline (R-(-)-deprenyl: a new therapeutic concept in the treatment of Parkinson's disease. *J Neural Transm* 1987;25:(suppl)1-197.
5. Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease: experience with this type of monoamine oxidase inhibitor in 200 patients. *Arch Neurol.* 1989;46:1280-1283.
6. Langston JW, Irwin I, Langston EB, Forno LS. Pargyline prevents MPTP-induced parkinsonism. *Science.* 1984;225:1480-1482.
7. Heikkila RE, Manzino L, Duvoisin RC, Cabbat FS. Protection against the dopaminergic neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) by monoamine oxidase inhibitors. *Nature.* 1984;311:467-469.
8. Cohen G, Pasik P, Cohen B, Leist A, Mytilineou C, Yahr MD. Pargyline and deprenyl prevent the neurotoxicity of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in monkeys. *Eur J Pharmacol.* 1984;106:209-210.
9. Cohen G. Monoamine oxidase, hydrogen peroxide, and Parkinson's disease. *Adv Neurol.* 1986; 45:119-125.
10. Cohen G, Spina MB. Deprenyl suppresses the oxidant stress associated with increased dopamine turnover. *Ann Neurol.* 1989;26:689-690.
11. Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline use to prevent progression of Parkinson's disease: experience in 22 de novo patients. *Arch Neurol.* 1989;46:1275-1279.
12. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science.* 1989;245:519-522.
13. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1989;321:1364-1371.
14. Yahr MD, Duvoisin RC, Mendoza MR, Schear MJ, Barrett RE. Modification of L-dopa therapy of parkinsonism by alpha-methyl-dopahydrazine (MK-486). *Trans Am Neurol Assoc.* 1971;96:55-58.
15. Libman I, Gawd MJ, Riopelle RJ, Bouchard S. A comparison of bromocriptine (Parlodel) and levodopa-carbidopa (Sinemet) for treatment of 'de novo' Parkinson's disease patients. *Can J Neurol Sci.* 1987;14:576-580.
16. Rinne UK. Combined bromocriptine-levodopa therapy early in Parkinson's disease. *Neurology.* 1985;35:1196-1198.
17. Rinne UK. Early combination of bromocriptine and levodopa in the treatment of Parkinson's disease: a 5-year follow-up. *Neurology.* 1987;37:826-828.
18. Heikkila RE, Huang J, Ofori S, Geller HM, Nicklas WJ. Potentiation by the tetraphenyl boron anion of the effects of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and its pyridium metabolite. *J Neurochem.* 1990;54:743-750.
19. Schapira AVH, Cooper JM, Dexter D, Clarke JB, Jenner P, Marsden CD. Mitochondrial complex I deficiency in Parkinson's disease. *J Neurochem.* 1990;54:823-827.

Ideomotor Apraxia in Huntington's Disease

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• The pattern of movement errors in ideomotor apraxia suggests an abnormality in selection and sequencing of component movements. Individuals with Huntington's disease were evaluated prospectively for the presence of apraxia, and aspects of motor and cognitive function were correlated with apraxic errors. Based on a conservative apraxia rating, ideomotor apraxia occurred in three (33%) of nine patients with a mean duration of disease of 10.4 years. Only two (22%) individuals made no apraxic errors, however, and the group as a whole made apraxic errors in 26% of movements. Apraxia was associated with errors in imitation of nonsymbolic movements but not with errors in recognition of gestures. It correlated significantly with duration of disease and with progressive abnormalities of posture but not with other individual aspects of elementary motor or cognitive function. These associations indicate that apraxia in Huntington's disease may be due primarily to involvement of subcortical motor structures rather than cerebral cortex.

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Ideomotor apraxia is a disorder of the performance of previously learned complex movements that cannot be ascribed to deficits in elementary motor function.[1,2] The performance of movements in an appropriate context and with real objects is characteristically better than propositional performance in individuals with ideomotor apraxia. Errors occur in symbolic movements, or gestures and pantomime, and it has been considered a disorder of symbolic behavior related to language (Goldstein, 1948). However, the imitation of novel nonsymbolic movements and the spontaneous production of previously learned nonsymbolic skilled movements, such as the use of a real tool, are also abnormal.[3,4] Ideomotor apraxia is highly associated with aphasia due to lesions of the language-dominant hemisphere, but both aphasia and apraxia may occur in isolation, suggesting that rather than being related disturbances of symbolic behavior, language and the production of learned movements are independent functions mediated by similar cerebral areas.

Several studies indicate that the imitation of nonsymbolic novel movements by apraxic subjects may actually be worse than imitation of symbolic movements and that this pattern may occur more often with lesions of the nondominant hemisphere.[3,5,6] Furthermore, error patterns in individuals with right or left hemisphere lesions do not appear to differ.[7] Together these findings suggest that ideomotor apraxia is a disorder of the formulation of complex and previously learned actions rather than of the ability to use symbols per se; ie, it is a disorder of motor programming.[1] Error pattern analyses for previously learned movements in patients with ideomotor apraxia suggest abnormal integration of component movements into a complete and appropriately timed sequence.

Based on evidence that the basal ganglia are involved in the formulation and coordination of complex previously learned motor routines, and on the evidence that ideomotor apraxia is a disorder of motor programming rather than symbol use per se, it is reasonable to expect disorders primarily affecting the basal ganglia to cause ideomotor apraxia. Therefore, we prospectively evaluated individuals with Huntington's disease (HD) for the presence of ideomotor apraxia.

SUBJECTS AND METHODS

Subjects

Apraxia was evaluated in three groups of individuals: patients with HD, a control group with senile dementia of the Alzheimer type (SDAT), and a group of normal controls. The individuals with HD had all been evaluated at the HD clinic at Hennepin County (Minn) Medical Center. Diagnosis was assigned on the basis of neurologic and behavioral symptoms and signs, appropriate family history, findings of computed tomography or magnetic resonance imaging, and the natural history of the disorder.[8-12] Criteria for diagnosis included the presence of chorea, dystonia, rigidity, and akinesia or the gradually progressive characteristic disorder of voluntary movement, not present at birth and of insidious onset. Emotional disturbances, memory loss, and other cognitive disturbances were present in most subjects. All patients seen in the clinic by the investigators during the study period and individuals seen previously and residing in a personal care center were eligible. Informed consent was obtained from 12 patients with HD and their legal guardians.

The subjects with SDAT were selected from among residents in a different personal care center. All residents with an admitting diagnosis of senile dementia, primary degenerative dementia, or Alzheimer's disease for whom consent could be obtained were screened using NINCDS-ADRDA criteria for SDAT.[13] Of 12 such individuals, only six met the criteria for probable SDAT. The SDAT control group was chosen because apraxia is known to occur in the disease and is associated with pathologic changes in the cortex. Measures of praxis and cognitive function used in the

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study were validated in this group.

Finally, 20 normal controls were selected from medical and orthopedic inpatient services. The age range included that of both patient groups, and none of the subjects had evidence of active central nervous system disease. Exclusion criteria included a history of stroke, dementia, or functionally significant memory impairment; moderate or severe hypertension; diabetes; syncope; brain tumor or systemic malignancy; significant head trauma; recurrent seizures; central nervous system infection; collagen vascular disease; and the use of psychoactive medications.

Table 1.—Auditory Comprehension Test*

1. Raise your hand.
2. Turn your head, then close your eyes.
3. Clap your hands, then look at the floor and touch your nose.
4. Touch the paper clip.
5. Touch the coin, then the pen.
6. Touch the fork, then the keys, and then the pen.
7. Touch the smallest object.
8. Put the pen between the coin and the keys.
9. Touch the pen with the fork.
10. Put the keys on top of the paper clip and pick up the coin.
11. Touch all of the objects.
12. Instead of the keys, pick up the pen.

*Based on an array of five objects: pen, fork, paper clip, penny, and keys. Scoring: 1, correct response; ½, repeat command once, correct response; and 0, incorrect or no response.

Procedures

The evaluation of all patients included a complete neurologic examination and history regarding the onset of illness, initial manifestations, and course. The family history was obtained from the patient's spouse, sibling, or occasionally a parent. The patient's age at onset of the first manifestations of HD or SDAT, duration of illness at the time of entry into the study, years of education, occupation, sex of the patient from whom the disease was inherited, and medications were recorded. Family history and formal pedigree were obtained by a geneticist, and vertical transmission, often with affected sibs, was documented. In only one individual with HD was the propositus the sole affected member in the pedigree, and this subject was subsequently excluded from the analysis of the results of the study (HD patient 11). Only one subject with probable SDAT had a positive family history with a mother who became demented at 70 years of age (SDAT patient 6).

Overall functional disability in all subjects was assessed according to Shoulson and Fahn's (1979) staging system for HD, in which individuals at stage 1 are employed at their usual level, and at stage 5 require total institutional care.[14]

A 14-item quantitative motor examination[10,15] was used to assess motor disability in patients with HD, and the scores on nine major aspects of motor function, scored 0 through 3 or 0 through 4 (ie, chorea, dystonia, rigidity, bradykinesia, dysdiadochokinesia, posture, speech, saccadic eye movement, and impersistence) were summed to create a composite score, the motor disability score, where a score of 0 indicates normal motor function and 32 indicates the maximum degree of motor dysfunction. Chorea was assessed in six different body segments and under five different conditions, giving a total of 30 scores per subject. To facilitate comparisons, an average measure of degree of chorea was derived from these data, the mean chorea score. This was the average of right and left upper limb and bucco-orolingual chorea in both seated and stressed conditions, with a score of 0 indicating the absence of chorea and 4 indicating a marked degree in terms of both amplitude and frequency.

An estimate of the degree of dementia was obtained with the Mini-Mental State examination (MMSE).[16] Other neuropsychological measures were designed to evaluate aspects of cognitive function that are of theoretical importance for the organization of symbolic motor behavior. A test of auditory comprehension similar to the Token Test[17] was devised, with easily discriminable test items (objects that were used in the formal apraxia test) and with less memory loading (Table 1). The 12 items included tests of single word comprehension, two- and three-stage sequential commands, and five items testing syntax comprehension.

Ideomotor apraxia was assessed in a standardized manner. Abnormal movements were scored as apraxic if (1) no obvious choreiform or dystonic movements coincided with the response; (2) the response did not correct after verbal instructions were repeated once (eg, if the subjects used a body part as object, they were instructed to pretend that they were actually holding the object); (3) comprehension of the command could be documented by having the subjects repeat the instructions or select the tool they were asked to use from a set of six; and (4) if the error conformed to one of the predetermined apraxic patterns. Error types were defined according to symbolic content, distal and proximal movements, postural fixation, and errors in timing and sequence of movements. Eight error types were thereby defined: (1) symbolic content errors, where the target movement was a recognizable gesture or pantomime but not appropriate for the gesture or tool requested; (2) body part-as-object, where the subject substitutes his or her own hand for the object rather than manipulating an imaginary object; (3) hand posture errors, where the configuration of the hand is inappropriate or fails to accommodate the imagined tool, but the movement of the limb is recognizable and appropriate for the target gesture or tool; (4) spatial orientation errors, a movement error where the hand posture or grip is correct but the movement is not directed to an appropriate target or is otherwise improperly oriented in space; (5) motor sequencing errors, where components of a limb movement are carried out in an improper or inconsistent order; (6) perseverative errors, where the immediately preceding gesture or pantomime is repeated; (7) onomatopoeic errors, where the verbal description of the action is substituted for the actual movement, eg, "blow"; and (8) imprecision errors, where the movement is inaccurate but the essential aspects of the action are recognizable.

Table 2.—Ideomotor Apraxia Test Items

Transitive limb
  1. Use a key
  2. Use a hammer
  3. Comb your hair
  4. Brush your teeth
  5. Screwdriver
  6. Scissors
  7. Use an eraser
  8. Throw a ball
  9. Flip a coin
  10. Stir with a spoon
Intransitive limb
  11. Wave goodbye
  12. Hitchhike
  13. Salute
  14. Motion come here
Buccofacial
  15. Blow out a match
  16. Sip through a straw
  17. Stick out your tongue
  18. Blow a kiss
  19. Cough
Axial
  20. Roll over in bed, or stand up, or turn your head

Complete failure to carry out the command may be a manifestation of ideomotor apraxia, but, for the purposes of this study, such errors were not scored because of the difficulty in documenting that they were indeed due to apraxia rather than to a failure to fully comprehend the instructions or to attend to the task. A priori, only body part-as-object errors, hand posture errors, and content errors as defined above were considered to be unequivocal apraxic errors, because the target action could be identified in each instance.

The formal ideomotor apraxia test included 20 test items: 10 transitive limb, four intransitive limb, five buccofacial, and one axial movement, which varied depending on the position of the subject at the time of examination (Table 2). The test was composed of four parts: (1) subjects first responded to a verbal command (propositional); (2) the examiner demonstrated three movements including the correct gesture and the subject identified the correct movement verbally, by number or by pointing; (3) subjects imitated the correct gesture, performed by the examiner, and any improvement in the response of the patient compared with propositional performance was recorded; and (4) subjects used the real object.

Three measures of apraxia were derived. The clinical rating was the assessment of the presence of apraxia in the standard screening neurologic examination performed at the time of entry into the study. When present, apraxia was rated as (1) mild, (2) moderate, or (3) severe, based on the frequency of errors and the occurrence with real objects. Second, a conservative estimate of the presence and degree of apraxia, the objective apraxia rating, was derived from the results of the formal apraxia test. Only unequivocal apraxic errors were considered in this rating, and all other errors were recorded but not scored. Subjects were assigned an apraxic rating only if they made three or more unequivocal apraxic errors, and the degree of apraxia was graded as follows: grade 1, three to five errors; grade 2, six to 10 errors; grade 3, 11 to 15 errors; and grade 4, 16 to 20 errors in the 20-item test. Third, all apraxic errors, major and minor, but excluding those scored as imprecision errors, were totaled for the total apraxic errors. Similarly, the total number of transitive and intransitive errors and of the total limb and buccofacial errors were analyzed.

An independent measure of the ability to imitate movement was devised to eliminate the influence of cuing inherent in the repeated exposure to the movements of the apraxia test and to compare ideomotor apraxia with impairment of performance of nonsymbolic movements. The items were similar to those used by De Renzi et al.[3,5] The examiner sat facing the subject and demonstrated 10 items that included four symbolic hand and finger movements (A-OK, victory, no-no, come here) and eight nonsymbolic novel movements, both categories including both fixed postures and movement sequences. The response was scored as correct or incorrect, and the total correct was recorded as the movement imitation score. Subjects were also asked to imitate Luria's two- and three-step motor sequences.

The normal controls were evaluated with the MMSE and the auditory comprehension, apraxia, movement imitation, movement recognition, and Luria's motor sequencing tests. The scores of the three study groups were compared by repeated measures analysis of variance for age, education, MMSE score, auditory comprehension score, all measures of ideomotor apraxia, and movement imitation. The patient groups were also compared in terms of duration of disease and functional disability rating. Significant differences thus identified by analysis of variance were evaluated by two-sample t tests with separate variance in a pairwise manner.

Finally, the scores of the HD group on all measures of ideomotor apraxia were compared by calculating Spearman rank correlation coefficients. Correlation coefficients were similarly calculated between the apraxia scores and all other measures of motor and cognitive function.

RESULTS

The clinical characteristics of the 12 subjects with HD are indicated in Tables 3 and 4. As the tables demonstrate, the HD group presents a broad range of disability, and the pattern of motor involvement is characteristic of the disease in general. One individual with HD had the predominantly rigid form of the disease (8%). No difference in age of onset was demonstrated according to sex of the affected parent, the mean age at onset being 39.0 years for male inheritance and 38.7 years for female inheritance (data were unavailable for two subjects). The HD and SDAT groups differed significantly in age (F[1,17] = 18.45; $P < .002$) and age at onset (mean, 73.6 years for SDAT group), as expected, but the mean ages were typical of the respective disorders. The groups were similar in overall functional disability rating (mean, 4.0 for SDAT group), and both were in midcourse according to the respective mean durations of disease (mean, 5.6 years for SDAT group).[8-11] Because of the age disparity in the patient groups, normal controls were selected with a range of ages encompassing both patient groups. The resulting control group had a mean age differing significantly from either patient group. The normal subjects were divided into two groups (n = 10) according to age: those younger than 65 years and those 65 and older (mean age (±SD), 57.9 ±5.93 and 73.4 ± 4.48, respectively). The mean age of the HD group was less than 2 SD from that of the younger normal subgroup, and, similarly, the age of the SDAT group was not significantly different from that of the older normal subgroup. These normal subgroups did not differ with respect to MMSE scores ($P > .29$), comprehension ($P = 1.0$), praxic errors ($P > .62$), movement recognition ($P > .56$), movement imitation ($P > .72$), and motor sequencing ($P > .30$), and they were therefore combined for all subsequent comparisons with the patient groups.

Two subjects (HD patients 10 and 11) were excluded from subsequent analysis because comprehension of commands in the apraxia test could not be documented and the occurrence of ideomotor apraxia could not be adequately evaluated. One subject (HD patient 12) was excluded because she refused to complete all tests. Most subjects with HD were treated with neuroleptic medication, but there was no correlation between use or dose of medication and the presence or degree of bradykinesia or apraxia. Specifically, HD patient 1 was taking no medications. The total daily doses (in milligrams) of other medications were as follows: HD patient 2, clorazepate dipotassium (3.75); HD patient 3, haloperidol decanoate (4.5) and lorazepam (6); HD patient 4, haloperidol (2), oxybutynin chloride (15) and levothyroxine sodium (0.2); and HD patient 5, chlorpromazine hydrochloride (75) and molindone hydrochloride (30); and HD patient 8, haloperidol (10) and alprazoloam (2); HD patients 6, 7, and 9 took only haloperidol at doses of 6, 40, and 5 mg/d, respectively.

The results of the tests of praxic function for the nine remaining subjects with HD are indicated in Table 5, and a comparison of results for HD, SDAT, and normal control groups are presented in Table 6. According to the objective apraxia rating, the most conservative measure of apraxia in this study, three (33%) of nine patients with HD and one (17%) of the six patients with SDAT but none of the normal controls were apraxic. The proportion of apraxic patients with SDAT was lower than that generally reported, which may be due to the moderate degree of cognitive impairment in the group as a whole and to the strict criteria established for the presence of apraxia in this study. According to the analysis of variance, the patient groups differed from the normal controls significantly in MMSE scores (F[2,32] = 51.30; $P < .001$), auditory comprehension (F[2,30] = 22.28; $P < .001$), total apraxic errors (F[2,32] = 9.32; $P < .001$), motor sequencing (F[2,32] = 12.03; $P < .001$), and education (F[2,32] = 3.91; $P < .05$) but not in movement recognition (F[2,32] = 0.47; $P > .6$) or movement imitation (F[2,31] = 2.19; $P > .1$). Post hoc analysis of these results with two-sample t tests indicated that only the patients with HD differed from the normal controls in total apraxic errors ($t = 2.73$; $df = 8.1$; $P < .026$) and years of education ($t = 2.85$; $df = 19.4$; $P < .010$). Both the HD and SDAT groups differed from the normal controls in MMSE, comprehension, and motor sequencing scores (Table 6).

As a group, the patients with HD made apraxic errors in 26% of movements (total apraxic errors, 6.0 of 20) and subjects with SDAT made apraxic movements in only 12.5% of movements (total apraxic errors [mean], 2.5 of 20). The most frequent error type in patients with HD was hand posture errors (33%), followed by body part-as-object (26%), content (17%), spatial orientation (11%), and motor sequencing errors, onomatopoeic and imprecision errors each accounting for 4% of errors. It may be argued that in the setting of an established basal ganglia disorder only body part–as-object or content errors may be reliably distinguished from more elementary disorders of movement. When only these types of errors were analyzed, the patients with HD still made significantly more errors than did control subjects (F[1,27] = 13.635; $P < .001$).

All measures of apraxia were highly correlated with one another, including the most and least conservative measures, the objective rating, and the total errors (Spearman, $r = .86$; $P < .003$). The clinical rating correlated with the objective apraxia rating ($r = .92$; $P < .0004$), the total apraxic errors ($r = .84$; $P < .0042$), the number of transitive errors ($r = 0.85$; $P < .0033$), and the number of intransitive errors ($r = .71$; $P < .032$). The difference between patient groups in the frequency of occurrence of apraxia was not significant (total apraxic errors, F[1,14] = 2.32; $P > .15$). There was also no difference between the groups in transitive (F[1,14] = 1.66; $P > .22$) or intransitive (F[1,14] = 3.05; $P > .10$) movements.

The degree of apraxia in individual subjects with HD correlated significantly with the duration of HD (Fig 1) (total apraxic errors, $r = .68$; $P < .043$), posture ($r = .79$; $P < .011$) and move-

Table 3.—Clinical Characteristics of Patients With Huntington's Disease

Patient No./ Age, y	Age at Onset, y	Duration, y	Sex	Sex of Affected Parent	Education, y	Functional Disability Score (0-5)
1/72	62	10	F	M	11	3
2/38	36	2	F	. . .	15	2
3/31	21	10	M	M	10	4
4/65	47	18	F	F	12	4
5/55	30	25	M	F	12	4
6/67	60	6	M	F	11	3
7/32	26	7	M	M	12	4
8/41	26	16	M	F	14	3
9/57	47	10	M	M	12	4
10/46	34	17	F	F	12	5
11/61	49	12	F	. . .	10	5
12/52	35	17	F	F	12	4
Mean 51.4	39.4	11.7	. . .	. . .	11.9	3.8
SD 13.8	13.4	5.1	. . .	. . .	1.4	0.9

Table 4.—Motor and Cognitive Characteristics of Patients With Huntington's Disease*

Patient No.	Motor Disability (0-32)	Mean (0-4)	Dystonia (0-4)	Muscle Tone (0-3)	Hypomimia (0-4)	Posture (0-3)	RAM (0-3)	MMSE (0-30)	Memory (0-3)
1	13	2.3	3	1	1	1	1	23	1
2	5	2.0	1	1	0	0	1	26	1
3	15	3.3	3	1	4	1	2	17	3
4	9	1.2	0	3	3	2	1	16	1
5	23	2.7	3	2	1	3	3	17	2
6	8	1.0	0	3	1	0	1	16	0
7	16	1.8	2	0	2	1	2	21	1
8	9	1.3	2	2	3	0	2	26	2
9	12	2.0	0	2	2	0	1	22	. . .
10	26	2.0	2	2	4	3	3	4	0
11	22	1.5	3	2	2	1	3	6	0
12	13	2.0	2	2	0	1	2	25	1
Mean	14.3	1.9	. . .	. . .	. . .	. . .	. . .	18.3	1.1
SD	6.5	0.6	. . .	. . .	. . .	. . .	. . .	7.2	0.9

*RAM indicates rapid alternating movements (disdiadochokinesia); MMSE, Mini-Mental State examination; and numbers in parentheses, range of scores.

Table 5.—Praxis in Patients With Huntington's Disease*

Patient No.	Clinical Apraxia Rating (0-3)	Objective Apraxia Rating (0-4)	Total Apraxic Errors (0-20)	Transitive Movement Errors, %	Intransitive Movement Errors, %	Movement Imitation Errors, %	Gesture Recognition Errors, %
1	2	2	7	50	14	0	0
2	0	0	0	0	0	0	0
3	0	0	2	17	0	8	0
4	2	2	12	75	43	50	0
5	3	3	14	83	71	83	0
6	0	0	0	0	0	0	29
7	1	0	3	25	0	0	0
8	0	0	2	0	29	0	0
9	0	0	4	17	29	. . .	0
Mean	44.4†	33.3†	4.9	29.7	20.7	17.6	3.2
SD	. . .	. . .	5.1	32.2	24.8	31.6	9.7

*Numbers in parentheses indicate range of scores.
†Percentage

ment imitation (both nonsymbolic and symbolic movements) (transitive errors, $r = .73$; $P < .041$) (total apraxic errors, $r = .68$; $P < .065$). There was also a trend between degree of apraxia and degree of overall motor disability, ie, the composite motor disability score (transitive errors, $r = .65$; $P < .059$) (total apraxic errors, $r = 0.59$; $P < .096$) and functional disability rating (transitive errors, $r = .65$; $P < .059$) (total apraxic errors, $r = .62$; $P < .075$). There was no correlation between degree of apraxia and degree of chorea (total apraxic errors, $r = .28$; $P > .46$), dystonia ($r = .25$; $P > .50$), rigidity ($r = .17$; $P > .65$), bradykinesia ($r = .50$; $P > .16$), dysdiadochokinesia ($r = .22$; $P > .55$), speech ($r = .29$; $P > .44$), extraocular movements ($r = .48$; $P > .18$), or motor impersistence ($r = .46$; $P > .20$).

Finally, there was no correlation between the degree of apraxia in HD and measures of cognitive function including auditory comprehension (total apraxic errors, $r = .62$; $P > .13$) and MMSE ($r = .24$; $P > .52$). The subjects with HD performed uniformly well in movement recognition, and no subject was able to perform Luria's motor sequences.

Table 6.—Comparison of Performance of Patient Groups and Normal Control*

	Normal Controls		HD			SDAT		
	Mean	SD	Mean	SD	P†	Mean	SD	P†
Age y	65.7	9.46	50.9	15.7	<.03	81.2	3.43	<.001
Education, y	10.2	1.94	12.1	1.54	<.01	11.8	2.23	NS
MMSE (30)	28.7	1.46	20.4	4.10	<.001	12.0	7.27	<.003
Comprehension (12)	11.8	0.34	10.1	1.24	<.02	7.8	2.84	<.02
Apraxia score (20)	19.8	0.44	15.1	5.09	<.03	18.2	1.94	NS
Movement recognition (6)	5.9	0.37	5.8	0.67	NS	6.0	0.0	NS
Movement imitation (12)	11.6	0.60	9.9	3.80	NS	10.7	1.51	NS
Motor sequencing (2)	1.1	0.85	0.0	0.0	NS	0.0	0.0	NS

*HD indicates Huntington's disease; SDAT, senile dementia of the Alzheimer type; MMSE, Mini-Mental State examination; NS, not significant; and numbers in parentheses, maximum score.

†Two-tailed two-sample *t* tests with separate variances.

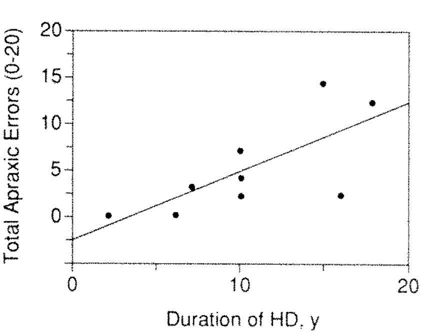

Fig 1.—Relationship between the degree of apraxia, as measured by total apraxic errors, and the duration of Huntington's disease (HD) in individual subjects.

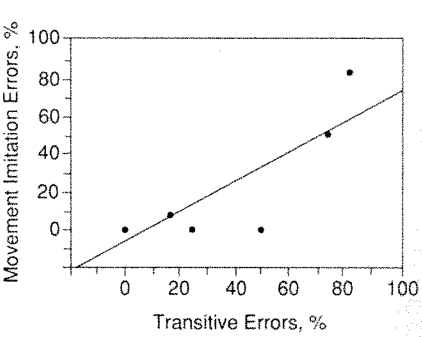

Fig 2.—Relationship between the degree of apraxia, as measured by the total number of transitive-movement errors, and imitation of symbolic and nonsymbolic movements. Data for the eight subjects who completed all tests are shown, but overlapping dots in the figure are not indicated.

COMMENT

The principal finding of this study is that ideomotor apraxia occurs in at least one third of individuals with HD. It is possible that the actual frequency is higher, as a rather conservative rating system was used in this study. In addition, those individuals who were severely impaired were excluded from the analysis, and it was impossible to determine the degree to which their failure to respond during testing resulted from apraxia as opposed to a failure to comprehend or attend to the commands. Seven (78%) of nine patients with HD made at least two apraxic errors, and it is possible that unequivocal apraxia would develop in such individuals with progression of the disease. If the maximum number of errors made by any normal subject on the apraxia test (one apraxic error) is accepted as the cutoff score between apraxic and nonapraxic subjects, two errors indicating the presence of apraxia (> 3 SD from the control group mean), then all of these individuals are apraxic. Similarly, three (50%) of the subjects with SDAT would be scored as apraxic.

Ideomotor apraxia has not previously been studied in HD. This is perhaps surprising because a variety of cognitive disorders including aphasia and neglect have been shown to result from subcortical as well as cortical lesions. Huntington's disease is associated with a variety of abnormalities in voluntary motor function, and involuntary movements may degrade or obscure target movements, complicating the interpretation of apraxia. This may in part explain the lack of information in the literature. The exclusion of deficits in elementary motor function is generally required for the diagnosis of apraxia. However, certain error types are characteristic of ideomotor apraxia and are recognizable even when degraded. For example, the use of a body part as object clearly identifies the target movement and indicates an error in the selection or symbolic content of the movement, permitting the demonstration of apraxia. In this study, apraxic errors were analyzed and, for the above reasons, only unequivocal apraxic errors were used in the assignment of apraxic status.

The pattern of apraxic errors in the patients with HD was similar to errors in apraxia following focal cerebral lesions.[7,18] The most common errors were body part-as-object, hand posture, spatial orientation, and content errors. In subjects with single unilateral cerebral infarctions, Rothi et al[18] found that the most frequent errors were body part-as-object, internal configuration (similar to hand posture errors here), external configuration orientation and external configuration movement (which together are similar to spatial orientation errors here), and content errors. The similar pattern in HD indicates that the errors were apraxic in nature and unrelated to chorea, dystonia, tremor, ataxia, or paresis. The patients manifested varying degrees of each of these movement disorders, but the presence of apraxia did not correlate with any of these, nor with bradykinesia or rigidity as assessed independently from the apraxia tests. Errors in the symbolic content of the movements and the fact that the movement errors were most frequent in the propositional setting and characteristically resolved when subjects used the real object also suggest that these errors were not due to abnormalities of elementary motor function.

Two varieties of ideomotor apraxia have been differentiated based on the ability of apraxic individuals to recognize and visually discriminate movements.[19] Those individuals with posterior parietal lesions or fluent aphasia are impaired in movement recognition compared with subjects with anterior lesions or nonfluent aphasia. It was proposed that the impairment of movement recognition results from destruction of visuokinesthetic engrams in the dominant inferior parietal cortex that encode the spatial characteristics, sequence, and timing of component movements. In HD, apraxia is therefore of the anterior type, with preservation of movement discrimination. This is consistent with the known relationships between the striatum, the initial and major focus of pathologic changes in HD, and the frontal association cortices. Early cognitive deficits in HD include decreased concentration, apathy, impairment of spontaneous initiation of activity, poor social judgment, organization and planning of sequential tasks, decreased verbal fluency, maze tracing, visual tracking, and abnormalities of narrative language or discourse, all suggesting abnormalities of frontal lobe function.[20-25] A similar pattern of deficits occurs following focal caudate infarction.[26]

The striatum is functionally associated with frontal lobe structures. While the basal ganglia receive afferents from virtually every cortical area, the putamen appears to be part of a functionally segregated circuit, receiving its principal input from primary motor, supplementary motor, premotor, and somatosensory cortices. Its principal output is to the supplementary motor cortex via ventral anterior and ventral lateral thalamic nuclei. The caudate receives its principal input from the frontal association cortex, and its output is to dorsolateral prefrontal, orbitofrontal, and anterior cingulate cortices.[27] The basal ganglia appear to be involved in nearly all types of movement, including self-paced or internally generated spontaneous movements and stimulus-triggered movements, including both ballistic and slow pursuit movements.[27-29] The supplementary motor area appears to be involved in the initiation of movement and in motor planning, as supplementary motor area lesions result in akinesia and mutism, and cerebral blood flow and electrophysiologic activity of the supplementary motor area increase in a specific manner preceding voluntary movement.[30-34] Furthermore, bilateral ideomotor apraxia has been demonstrated in association with lesions of the left supplementary motor area.[35] It is important to note that putaminal neuronal activity similarly changes in relation to movement instructions in preparation for movement, and the basal ganglia may therefore have a role in motor planning similar to that of the supplementary motor area.[36]

Individuals with Parkinson's disease characteristically have difficulty with initiation of movement and in sustaining multiple simultaneous actions, but responses may be substantially improved with external cues.[37] Marsden[38] proposed that the basal ganglia are involved in "the automatic execution of learned motor plans," requiring the sequential or concurrent operation of a number of simple motor programs. More recently, Thompson et al[39] have demonstrated similar difficulty in the performance of sequential and concurrent movements in HD. Ideomotor apraxia in HD may therefore be caused by abnormalities in the interaction between the abnormal basal ganglia and unaffected premotor cortical structures more commonly associated with apraxia, resulting from a dissolution of such aspects of motor programming. This would indicate further that basal ganglia processing is required for the performance of symbolic movements and that the interaction between parietal cortex and frontal association cortex alone is insufficient. The subjects with SDAT were less apraxic and more demented than those with HD (according to MMSE and auditory comprehension scores), a double dissociation in cognitive deficits. This finding suggests that the mechanism of apraxia in HD differs from the disruption of cortical processing presumed to be the cause of apraxia in SDAT.[40]

On the basis of this study, it cannot be determined whether the apraxia was due to involvement of frontal cortex or to involvement of subcortical structures alone. In early stages of HD, the caudate head is selectively involved and progresses to involve the putamen, the globus pallidus, and subthalamic and certain thalamic nuclei. In late stages of the disease, structural changes in the cerebral cortex have been documented in some individuals, primarily neuronal loss and mild gliosis in deeper layers of the frontal cortex.[41] Several of the subjects in the present study who made apraxic errors were only mildly impaired in terms of cognitive function (HD patients 7, 8, and 9). Fluorodeoxyglucose positron emission tomography and computed tomographic studies have demonstrated that early dementia in HD is associated with hypometabolism of the caudate head but not with atroph or hypometabolic changes in the cerebral cortex.[42] It appears, therefore that ideomotor apraxia occurs in H at a stage when cortical structures ar not implicated in the degenerative process, lending support to the hypothesi that apraxia may result from basa ganglia lesions alone.

Ideomotor apraxia is most often du to focal lesions of the dominant inferior parietal lobe and is therefore associated with disturbances of languag comprehension. The preservation o auditory comprehension and the lac of correlation between the occurrenc of apraxia and comprehension tes scores in this study at first suggeste that subcortical disease was responsible for the apraxia. As indicated above however, ideomotor apraxia also results from lesions restricted to premotor association cortex or to subcortical white matter connections between premotor and inferior parietal areas. As there was no independent discrete measure of frontal association cortex function, the possibility of frontal, exclusive of parietal, cortical involvement remains unresolved.

Mild ideomotor apraxia was previously reported in association with focal infarction of basal ganglia, thalamus, and internal capsule in either the right or the left hemispheres. An analysis of apraxic errors was not performed in this study,[43] however, and a comparison with the pattern of ideomotor apraxia in the present study is not possible.

To conclude, it appears that certain aspects of the apraxias, which are considered to be disorders of higher cortical function, result from the disruption of basal ganglia input. In this regard, it has been demonstrated that putaminal activity increases in relation to instructions for movement alone and that the basal ganglia play a significant role in the initiation of voluntary movement.[34,35] Error pattern analyses indicate that a majority of apraxic errors are not errors of symbolic content but represent a failure to combine individual proximal and distal limb movements either concurrently or in sequence. This is consistent with the common abnormalities of motor control seen in basal ganglia disorders.[27-38]

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References

1. Heilman KM, Rothi LJ. Apraxia. In: Heilman KM, Valenstein E, eds. *Clinical Neuropsychology.* 2nd ed. New York, NY: Oxford University Press Inc; 1985:131-150.

2. Geschwind N, Damasio AR. Apraxia. In: Frederiks JAM, ed. *Handbook of Clinical Neurology, Vol. 1 (45): Clinical Neuropsychology.* New York, NY: Elsevier Science Publishing Co Inc; 1985:423-432.

3. De Renzi E, Motti F, Nichelli P. Imitating gestures. *Arch Neurol.* 1980;37:6-10.

4. De Renzi E, Faglioni P, Sorgato P. Modality-specific and supramodal mechanisms of apraxia. *Brain.* 1982;105:301-312.

5. De Renzi E, Pieczuro A, Vignolo LA. Ideational apraxia: a quantitative study. *Neuropsychologia.* 1968;6:41-52.

6. Kimura D, Archibald Y. Motor functions of the left hemisphere. *Brain.* 1974;97:337-350.

7. Haaland KY, Flaherty D. The different types of limb apraxia errors made by patients with left vs right hemisphere damage. *Brain Cogn.* 1984; 3:370-384.

8. Conneally MP. Huntington's disease: genetics and epidemiology. *Am J Hum Genet.* 1984; 36:506-526.

9. Marx RN. Huntington's chorea in Minnesota. *Adv Neurol.* 1973;1:237-249.

10. Young AB, Shoulson I, Penny JB, et al. Huntington's disease in Venezuela: neurologic features and functional decline. *Neurology.* 1986;36:244-249.

11. Folstein SE, Leigh RJ, Parhad IM, Folstein MF. The diagnosis of Huntington's disease. *Neurology.* 1986;36:1279-1281.

12. Myers RH, Martin JB. Huntington's disease. *Semin Neurol.* 1982;2:365-372.

13. McKhann G, Drachman D, Folstein MF, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.

14. Shoulson I. Care of patients and families with Huntington's disease. In: Marsden CD, Fahn S, eds. *Movement Disorders.* Stoneham, Mass: Butterworths; 1982:277-290.

15. Shoulson I, Goldblatt D, Charlton M, Joynt RJ. Huntington's disease: treatment with muscimol, a GABA-mimetic drug. *Ann Neurol.* 1978; 4:279-284.

16. Folstein MF, Folstein SE, McHugh P. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

17. De Renzi E, Vignolo LA. The Token Test: a sensitive test to detect receptive disturbances in aphasia. *Brain.* 1962;85:665-678.

18. Rothi LJG, Mack L, Verfaellie M, Brown P, Heilman KM. Ideomotor apraxia: error pattern analysis. *Aphasiology.* 1988;2:381-388.

19. Heilman KM, Rothi LJ, Valenstein E. Two forms of ideomotor apraxia. *Neurology.* 1982; 32:342-346.

20. Butters N, Sax D, Montgomery K, Tarlow S. Comparison of the neuropsychological deficits associated with early and advanced Huntington's disease. *Arch Neurol.* 1978;35:585-589.

21. Caine ED, Bamford KA, Schiffer RB, Shoulson I, Levy S. A controlled neuropsychological comparison of Huntington's disease and multiple sclerosis. *Arch Neurol.* 1986;43:249-254.

22. Kennedy J, Fisher L, Shoulson I, Caine E. Language impairment in Huntington's disease. *Neurology.* 1981;31:81-82.

23. Moss MB, Albert MS, Butters N, Payne M. Differential patterns of memory loss among patients with Alzheimer's disease, Huntington's disease, and alcoholic Korsakoff's syndrome. *Arch Neurol.* 1986;43:239-246.

24. Butters N, Albert MS, Sax D. Investigations of the memory disorders of patients with Huntington's Disease. *Adv Neurol.* 1979;23:203-213.

25. Brouwers P, Cox C, Martin A, Chase T, Fedio P. Differential perceptual-spatial impairment in Huntington's and Alzheimer's dementias. *Arch Neurol.* 1984;41:1073-1076.

26. Mendez MF, Adams NL, Lewandowski KS. Neurobehavioral changes associated with caudate lesions. *Neurology.* 1989;39:349-354.

27. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Ann Rev Neurosci.* 1986;9:357-381.

28. DeLong MR, Georgopoulos AP. Motor functions of the basal ganglia. In: Brookhart JM, Mountcastle VB, Brooks VB, eds. *Handbook of Physiology: The Nervous System.* Bethesda, Md: American Physiological Society; 1981:1017-1061.

29. DeLong MR, Georgopoulos AP, Crutcher MD. Cortico-basal ganglia relations and coding of motor performance. *Exp Brain Res.* 1983 (suppl);7:30-40.

30. LaPlane D, Talairach J, Meininger V, Bancaud J, Orgogoza JM. Clinical consequences of corticectomies involving the supplementary motor area in man. *J Neurol Sci.* 1977;34:301-314.

31. Masdue JC, Schoene WC, Funkenstein H. Aphasia following infarction of the left supplementary motor area. *Neurology.* 1978;28:1220-1223.

32. Roland PE, Larsen B, Lassen NA, Skinhøj E. Supplementary motor area and other cortical areas in organization of voluntary movements in man. *J Neurophysiol.* 1980;43:118-136.

33. Tanji J, Taniguchi K, Saga T. Supplementary motor area: neuronal response to motor instructions. *J Neurophysiol.* 1980;43:60-68.

34. Evarts EV, Wise SP. Basal ganglia outputs and motor control. In: Evered D, O'Connor M, eds. *Functions of the Basal Ganglia.* London, England: Pitman Publishing; 1984:83-96. Ciba Foundation Symposium 107.

35. Watson RT, Fleet WS, Gonzales-Rothi L, Heilman KM. Apraxia and the supplementary motor area. *Arch Neurol.* 1986;43:787-792.

36. Alexander GE. Instruction-dependent neuronal activity in primate putamen. *Soc Neurosci Abstr.* 1984;10:515.

37. Martin JP. *The Basal Ganglia and Posture.* London, England: Pitman Publishing; 1967.

38. Marsden CD. The mysterious motor function of the basal ganglia: the Robert Wartenberg Lecture. *Neurology.* 1982;32:514-539.

39. Thompson PD, Berardelli A, Rothwell JC, et al. The coexistence of bradykinesia and chorea in Huntington's disease and its implications for theories of basal ganglia control of movement. *Brain.* 1988;111:223-244.

40. Sjögren T, Sjögren H, Lindgren AGH. Morbus Alzheimer and morbus Pick. *Acta Psychiatr Neurol Scand.* 1952;3(suppl 82):1-152.

41. Tomlinson BE, Corsellis JAN. Ageing and the dementias. 4th ed. In: Adams JH, Corsellis JAN, Duchen LW, eds. *Greenfield's Neuropathology.* New York, NY: John Wiley & Sons Inc; 1984:951-1025.

42. Kuhl DE, Phelps ME, Markham CH, Metter EJ, Reige WH, Winter J. Cerebral metabolism and atrophy in Huntington's disease determined by 18 FDG and computed tomographic scan. *Ann Neurol.* 1982;12:424-434.

43. Agostoni E, Coletti A, Orlando G, Tredici G. Apraxia in deep cerebral lesions. *J Neurol Psychiatry.* 1983;46:804-808.

Initial Therapy of Patients With Wilson's Disease With Tetrathiomolybdate

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• Patients with Wilson's disease who present with acute neurological symptoms often become clinically worse when initially treated with penicillamine. Other available anticopper drug therapies do not appear to offer a solution to this treatment problem. We are developing and evaluating a new drug, ammonium tetrathiomolybdate for this purpose. Theoretically, tetrathiomolybdate has optimal properties, including an immediate blockade of copper absorption and the property of forming complexes with copper in the blood, rendering the copper nontoxic. In this article, we present results from six patients treated with tetrathiomolybdate for up to 8 weeks as initial therapy. None of the five patients who had presented with acute neurological symptoms worsened. Also presented are methods of assay, preliminary stability studies, and methods of evaluating therapeutic end points with respect to copper metabolism.

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The anticopper therapy of patients presenting with symptomatic Wilson's disease can be broken down as occurring in two phases. The first is the initial treatment phase, generally thought of as the period when toxic copper levels are brought under control so that further copper toxicity is abated. The second is the maintenance treatment phase, which is the lifelong prevention of the reaccumulation of copper to toxic levels. Any one of three drugs—zinc, penicillamine, or trien—can be used for maintenance therapy with complete efficacy.[1,2] These three drugs differ for this use only in the number and severity of side-effects and in the extent of recorded experience. In contrast with this relatively comfortable situation for maintenance therapy, a satisfactory approach for the initial treatment of symptomatic patients has not been worked out, in our opinion.

This hiatus in therapy is most apparent for the patient who presents with neurological symptoms from Wilson's disease. We have anecdotally observed patients becoming much more severely affected neurologically when initially treated with penicillamine. A retrospective survey revealed that 13 of 25 patients presenting with neurological symptoms worsened within the first few weeks of therapy with penicillamine, and that six of these patients never recovered to the pretherapy baseline.[3] The mechanism of this penicillamine-induced neurological worsening is not clear but may involve redistribution of copper from other parts of the body into the brain, or within intracellular compartments.

At least theoretically, zinc therapy also does not appear to be the answer for this type of patient. It acts slowly and produces only a very modest negative copper balance.[4,5] It seems possible that the disease could progress to a certain extent during the several months that it takes to bring copper toxicity under control. Indeed, in one of three neurologically affected patients whom we treated with zinc, tremor did seem to progress over the first few months of therapy. There is very little experience with the third drug therapy, trien. Since its mechanism of action is somewhat similar to penicillamine, it may be subject to the same problem of neurological worsening.

We believe that ammonium tetrathiomolybdate may provide an answer for the initial treatment of the neurologically affected patient. This drug has two anticopper mechanisms of action.[6-9] One mechanism involves complexing copper, together with food proteins, in the gastrointestinal tract, preventing absorption of copper. The second mechanism is that absorbed tetrathiomolybdate forms complexes with copper and albumin in blood, rendering the copper unavailable for cellular uptake, and, therefore, removing it from toxic pools. Because of these promising properties, we have carried out pilot work using tetrathiomolybdate for the initial treatment of neurologically affected patients. Herein we report our observations with the first six patients whom we have treated with tetrathiomolybdate.

PATIENTS AND METHODS

Patients

The six patients involved in this study all had Wilson's disease, as established by criteria summarized in Table 1. The first five patients listed in Table 1 presented with acute neurological symptoms, as summarized in Table 1. The sixth patient (No. 38) had originally presented with neurological disease but had been treated for several years with penicillamine and later with zinc. Inexplicably, she stopped all treatment for many months and then presented to us with a copper status that was out of control. Her liver-derived serum enzyme levels were significantly elevated, compared with prior values. Because of concerns that neurological deterioration might develop at any time, we elected to treat her initially with tetrathiomolybdate. In three of the first five listed cases in Table 1 (cases 56, 63, and 68), the initial treatment was with tetrathiomolybdate. Patients 61 and 79 had been treated briefly with penicillamine and, because of concerns that their conditions were deteriorating, were referred to us for treatment with tetrathiomolybdate. All patients who participated in this study were hospitalized in the Clinical Research Center of the University of Michigan Hospital, Ann Arbor. Most patients were admitted for the entire time they received tetrathiomolybdate. All patients who participated in this study gave written informed consent. This research was carried out according to the principles of the Declaration of Helsinki (Finland) and approved by the Committee on the Use of Humans as Experimental Subjects of the University of Michigan.

Materials

Tetrathiomolybdate was purchased from Aldrich Chemical Co, Milwaukee, Wis, in a form suitable for human administration. It was stored in bulk form, anaerobically, protected from light, and at room temperature (*standard bulk storage*). At the time of admission of a patient who was to receive therapy with tetrathiomolybdate, the drug was weighed out in appropriate amounts

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Table 1.—Initial Clinical and Laboratory Observations

Patient No.	Sex	Age at Tetrathiomolybdate Initiation, y	Kayser-Fleischer Rings	Plasma Ceruloplasmin, mg/L	Plasma Copper, μmol/L	Copper in Liver, μg/g Dry Weight	Copper in Urine, μmol/d	Neurological Symptoms	Comment
56	M	36	Present	131	9.9	1621	3.4	Dysarthria; gait abnormalities; tremor; cerebellar; discoordination	...
61	M	16	Present	<10	7.5	1411	2.1	Dysarthria; tremor; dystonia; drooling; gait abnormalities	Treated initially with penicillamine for 6 wk
63	M	24	Present	130	12.4	391	3.4	Dysarthria; rigidity; gait abnormalities; dystonia	...
68	M	22	Present	<10	7.5	428	5.0	Dysarthria; rigidity; gait abnormalities; dystonia; tremor	White matter lesions on magnetic resonance imaging; developed seizures
79	M	32	Present	72	9.4	1228	5.2	Dysarthria; tremor; gait abnormalities; rigidity; dystonia	Treated initially with low doses of penicillamine for 4 wk
38	F	24	Present	<10	7.5	781	7.6	Dysarthria; gait abnormalities; drooling	Special case; patient receiving maintenance therapy who quit therapy and developed high copper values in urine

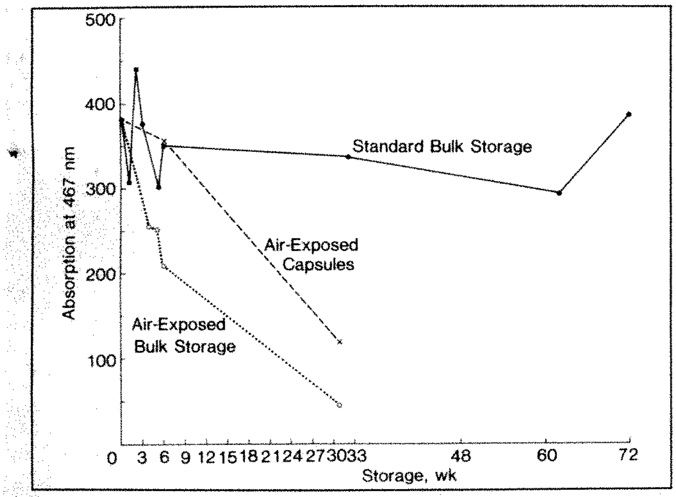

Fig 1.—For standard bulk storage, tetrathiomolybdate was kept in 100-g brown, sealed bottles at room temperature. For air-exposed bulk storage, a few grams of the powder were kept in a bottle with the top off at room temperature. For air-exposed capsules, capsules were kept in a bottle with the top off at room temperature. For assay, 10 μg of the drug was placed in 1.0 mL of distilled water, and absorption measured at 467 nm in a spectrophotometer (Gilford 2400S, Gilford Instrument Laboratories Inc, Oberlin, Ohio).

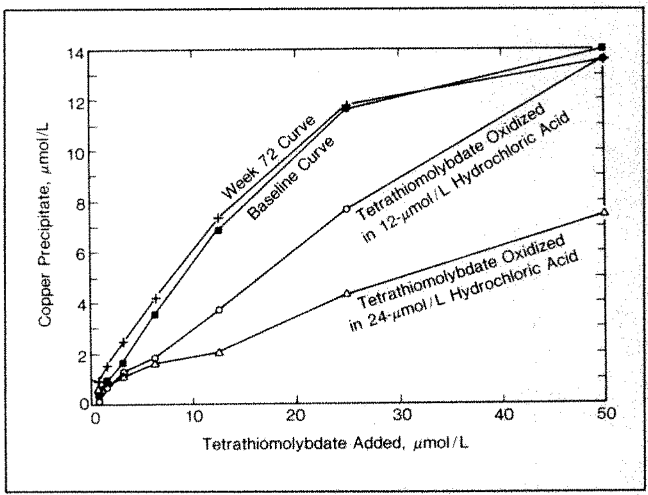

Fig 2.—This biological assay was carried out by adding the indicated amount of tetrathiomolybdate to 2.0 mL of 5.0 mmol/L-Hepes buffer containing 15 μmol/L of copper acetate and 150 μmol/L of human albumin. The mixture was allowed to stand for 15 minutes at room temperature. Then 2.0 mL of the mixture was mixed with 2.0 mL of the trichloroacetic acid solution, such that the final concentration of trichloroacetic acid was 5%. This mixture was shaken for 15 seconds in a Vortex mixer and then centrifuged at 1500 *g*. The copper concentration in the supernatant was assayed and subtracted from that added to determine the amount of copper precipitated. As a control, to show loss of tetrathiomolybdate biological activity under conditions of oxidation, tetrathiomolybdate treated with either 12 or 24 μmol/L of hydrochloric acid was also assayed.

Table 2.—Tetrathiomolybdate Therapy Data

Patient No.	Weight, kg	Final Dose		Dose Regimen Amount, mg*		Days Until Closure of Copper-Molybdenum Gap
		mg/d	mg/kg	With Meals	Between Meals	
56	97	150	1.6	20	30	15
61	62	180	2.9	20	40	17
63	87	210	2.4	30	40	11
68	51	150	2.9	20	30	14
79	93	220	2.4	20	60-60-40	29
38	45	90	2.0	10	20	8

*The tetrathiomolybdate was administered three times daily with meals, and three times daily between meals.

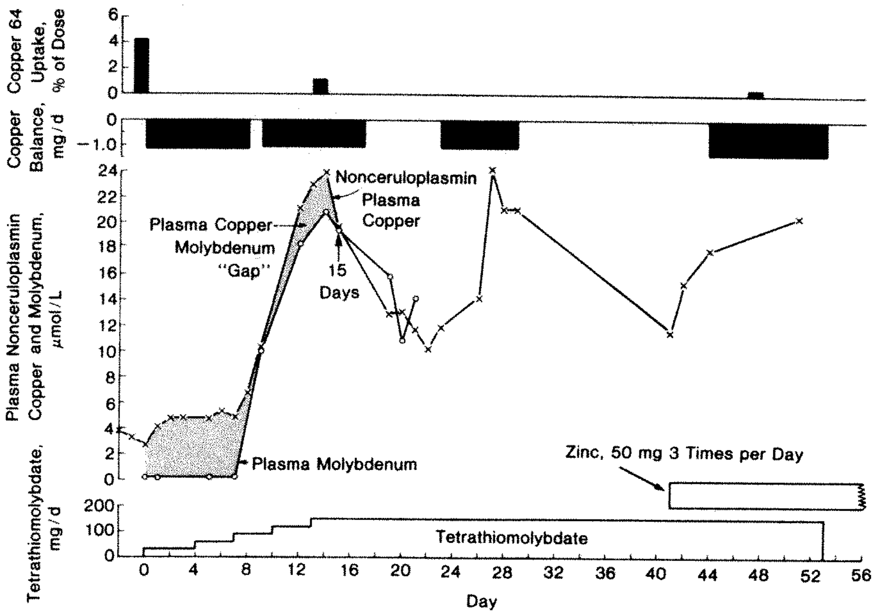

Fig 3.—Results of treatment of patient 56 with tetrathiomolybdate.

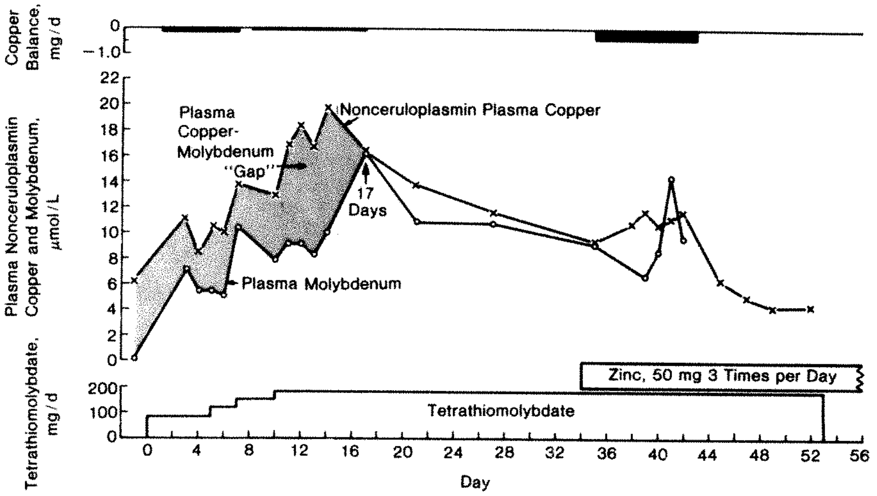

Fig 4.—Results of treatment of patient 61 with tetrathiomolybdate.

and placed in capsules by one of us (R.T.). Depending on the patient and dose prescribed, capsules contained 10, 20, 30, or 40 mg. The dose of drug was individualized in each case as experience was gained (Table 2). Details are provided in the "Results" section.

Methods

The stability and potency of tetrathiomolybdate was evaluated in several ways. The parent molecule has an absorption peak at 467 nm,[10] and this was followed over time (methodological details in the legend to Fig 1). In addition, a bioassay was developed that depended on rendering a stoichiometric amount of copper insoluble in trichloroacetic acid in the presence of albumin (methodological details in the legend to Fig 2). We also performed special studies examining the rate of degradation under conditions of patient usage and under conditions that were anticipated to make the drug degrade. These conditions will be defined in the "Results" section and in the figure legends.

End points for our therapeutic objectives related to copper needed to be defined to determine the dosage required. We had two proximal therapeutic objectives. One was to block absorption of copper in the gastrointestinal tract as soon as possible after therapy began. This end point was evaluated by established methods determining the absorption of orally administered copper 64[11] and by evaluating copper balance.[4,5] The second objective was to "neutralize" the potentially toxic copper levels in the blood as rapidly as possible. By *neutralize* we mean the binding of the potentially toxic copper to tetrathiomolybdate-albumin complexes, which renders the copper unavailable for cellular uptake. This effect was evaluated as follows: First, the total plasma copper and the ceruloplasmin activity were determined, and the calculated amount of ceruloplasmin-bound copper (3 µg of copper per milligram of ceruloplasmin) was subtracted from the total plasma copper level to determine the nonceruloplasmin plasma copper (NCPCu) level. Ceruloplasmin-bound copper is viewed as nontoxic. The NCPCu level is the potentially toxic copper and is the copper that needs to be "neutralized" by tetrathiomolybdate therapy. We then determined the total molybdenum content of the plasma and examined the stoichiometry of molybdenum to NCPCu, which should be 1:1 when all NCPCu is complexed to tetrathiomolybdate. Copper and molybdenum were assayed by atomic-absorption spectrophotometry (IL 451, Instrumentation Laboratory Inc, Wilmington, Mass). In one instance, an effect of treatment on mean excretion of copper in urine was evaluated for statistical significance using the paired *t* test.

It was critical during this study to determine the patient's clinical status to evaluate whether there was significant neurological deterioration during therapy with tetrathiomolybdate. This was achieved by two separate and independent evaluations, one of speech function and one of overall neurologic function. A baseline quantitative neurological examination was performed by one of us (A.B.Y.) using methods previously described,[12] another was conducted during the midpoint of the 8-week tetrathiomolybdate treatment, and a final one was performed at the end of the 8 weeks. The results of the initial and final examinations are reported here by a scoring system previously described[12] that quantitatively evaluates tremor, dysarthria, fine-motor coordination, resting dystonia, and rigidity. Worsening is depicted by a higher score, improvement by a lower score. Clinical motor speech function was evaluated with oral motor examinations, and perceptual speech analysis was documented with audiotape recordings. A speech pathologist (K.J.K.) analyzed and rated the severity of the dysarthria during the examination and from audiotaped samples of spontaneous speech, expository speech, oral reading of the "Grandfather Passage," diadochokinetic rates, verbal and nonverbal agility scores, counting from 1 to 75, and duration of the vowel sounds "ah" and "ee." We used the deviant speech dimensions defined by Darley et al.[13] A rating scale was devised extending from 0 (unaffected) to 6 (severely affected) for the severity of dysarthria. Initial examinations were performed within 2 to 4 days following admission and prior to initiation of therapy with tetrathiomolybdate. Examinations were repeated on a weekly basis during the administration of tetrathiomolybdate. The results of the initial and final examinations are reported here.

RESULTS

The results of the studies evaluating the potency and stability of tetrathiomolybdate under various storage conditions are shown in Figs 1 and 2. It is clear that with standard bulk storage the drug is quite stable, as measured both by absorption at 467 nm (Fig 1)

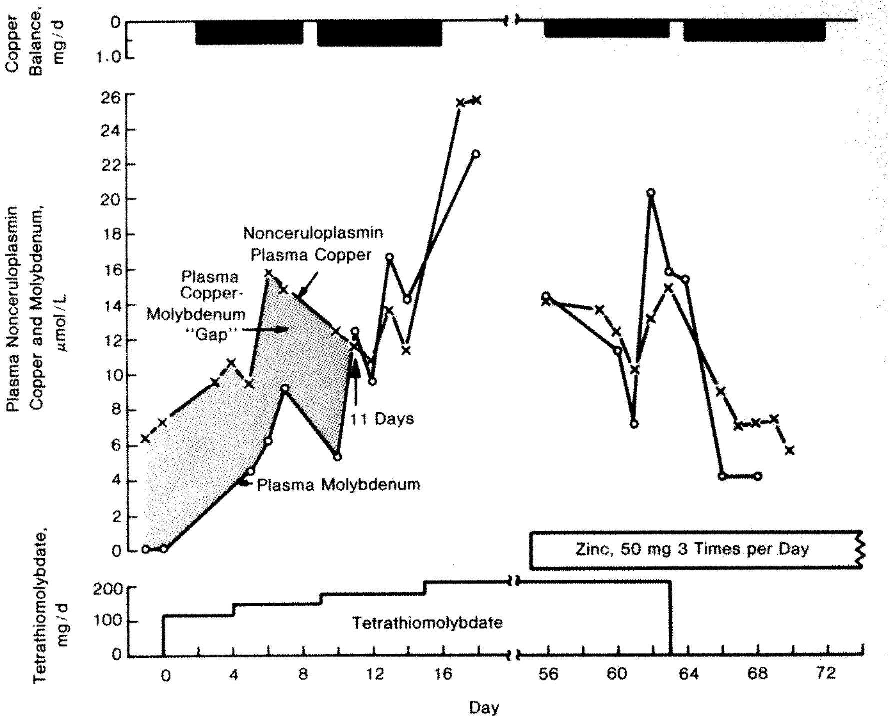

Fig 5.—Results of treatment of patient 63 with tetrathiomolybdate. This patient was discharged from the hospital for a period during the middle of the study but continued tetrathiomolybdate treatment at home.

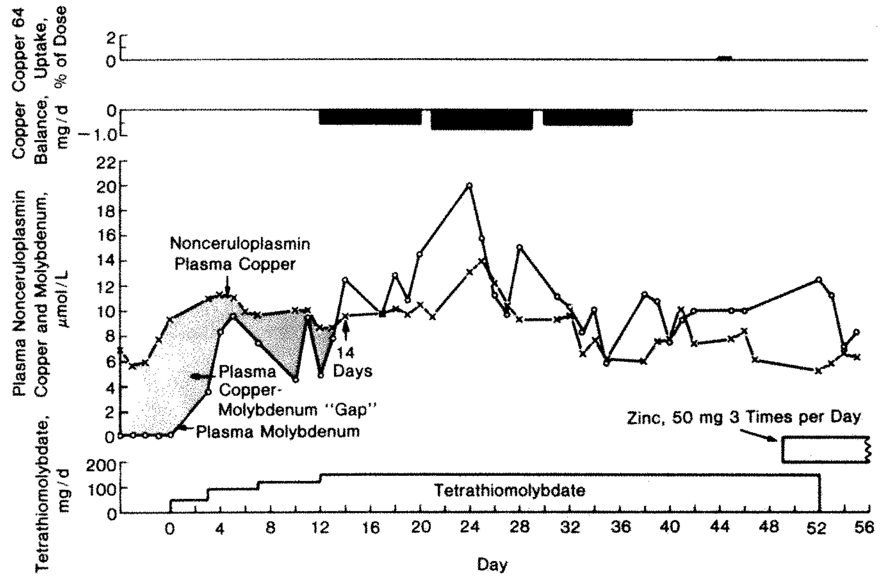

Fig 6.—Results of treatment of patient 68 with tetrathiomolybdate.

and by the amount of copper precipitated by a given concentration of tetrathiomolybdate in the bioassay (Fig 2) over the 72-week period of observation. On the other hand, exposure to air causes loss of most of the specific absorption by 31 weeks (Fig 1). However, we found that capsules stored in a pharmacy bottle at room temperature and opened repeatedly each day, as would be typical for patient use, were fully potent over an 8-week period (data not shown).

The results of the copper and molybdenum studies in the patients are shown in Figs 3 through 8. In the first patient studied (Fig 3) the initial dose was 10 mg administered three times per day with meals. This dose was escalated every 3 to 4 days until a daily dose of 150 mg (50 mg three times per day with meals) was reached. While the effect on producing a negative copper balance was immediate (Fig 3), not much effect on copper and molybdenum values was noted until the dose was divided such that half was given between meals, in a six times per day program (day 8, Fig 3). This resulted in a prompt increase in the total plasma copper level, much of which was insoluble in trichloroacetic acid (it is characteristic of tetrathiomolybdate-complexed copper to be trichloroacetic acid insoluble). The increase in the total plasma copper level was paralleled by an increase in the plasma molybdenum level. The ratio of NCPCu to molybdenum was close to unity by day 15 of therapy and thereafter (arrow, Fig 3). At no time did the patient's condition deteriorate clinically. Blockade of oral copper 64 uptake was demonstrated (Fig 3). After 6 weeks, zinc acetate therapy was added, and, after 2 weeks of concomitant therapy, tetrathiomolybdate therapy was stopped. The transition to zinc therapy was smooth. This patient has now received therapy with zinc for 2 years after initial treatment with tetrathiomolybdate and is almost fully recovered and living a normal life.

With subsequent patients (other than patient 38), the final dose was higher (Table 2), particularly on a per kilogram body-weight basis, because we wished to reach control of copper levels in the blood as quickly as possible. We also tended to shift a higher proportion of the dose to the between-meal fraction for the same reason (Table 2).

In patient 61 (Fig 4), the plasma copper-molybdenum gap was eliminated in 17 days. For unknown reasons, this patient's negative copper balance was smaller than in the other patients (Fig 4). The plasma copper-molybdenum gap was closed in 11 days in patient 63 (Fig 5) and in 14 days in patient 68 (Fig 6). Both of these latter patients showed consistent negative copper balances of about 0.5 mg/d or a little more. Patient 79 required 29 days to close the plasma copper-molybdenum gap (Fig 7). It is not clear why this patient took longer to reach this end point, although the patient did have the highest level of copper in the urine sample of the five patients receiving initial treatment (Table 1).

Patient 38 was the patient with a compliance problem with a very high initial level of copper in her urine sample (Table 1) and an NCPCu of about 7.5 µmol/L. Zinc was reinstituted as her maintenance therapy, and tetrathiomolybdate therapy was initiated as well. Her plasma copper-molybdenum gap was eliminated in 8 days (Fig 8). This patient had exhib-

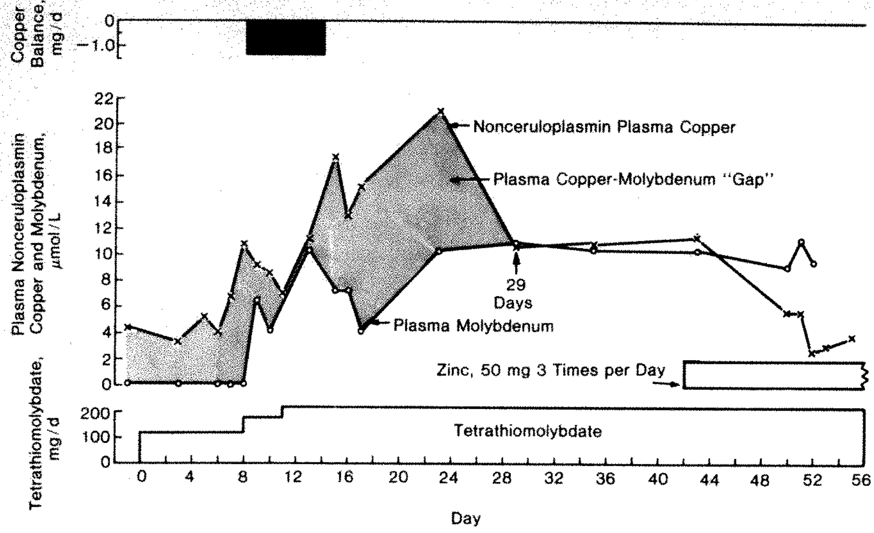

Fig 7.—Results of treatment of patient 79 with tetrathiomolybdate.

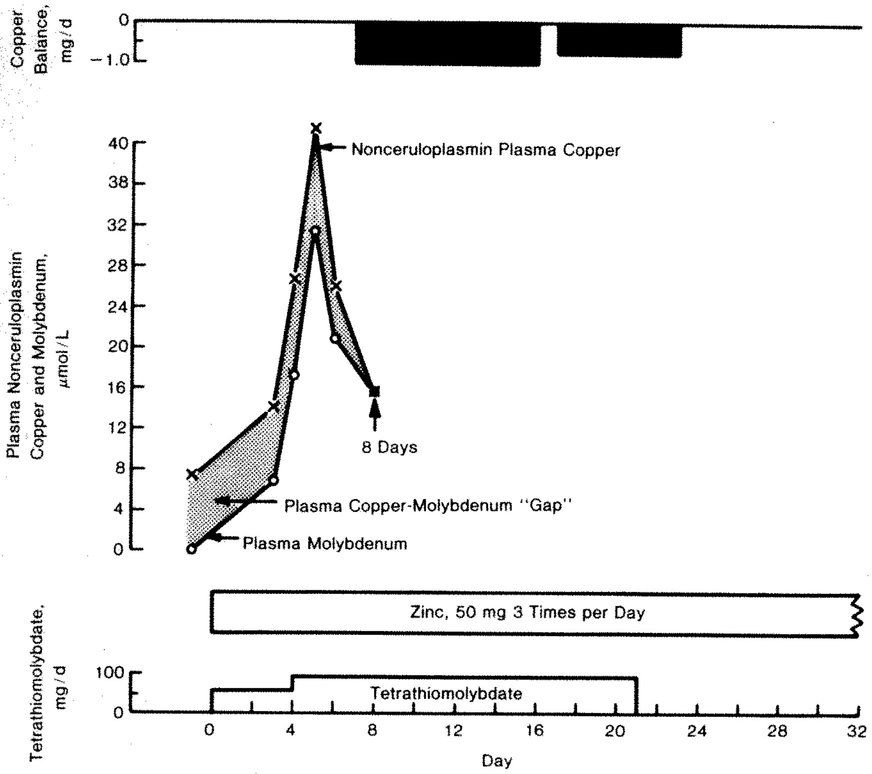

Fig 8.—As explained in the text, this patient had initially presented with neurological disease, but had long been treated with anticopper agents and was in the maintenance phase of therapy, with a stable clinical picture and mild-to-moderate neurological residual effects. She then inexplicably discontinued therapy. When admitted for a routine checkup, we found dangerously high urine, copper, and nonceruloplasmin plasma copper values and elevated liver-derived serum enzyme values. She was treated with a combination of zinc and tetrathiomolybdate, in an effort to prevent the development of new neurological symptoms.

ited liver copper toxicity in terms of elevated enzyme values, and these elevated enzyme values decreased quickly with the combined tetrathiomolybdate and zinc therapy (Table 3).

The rapid decrease in trichloroacetic acid-soluble copper in urine during the period of tetrathiomolybdate therapy in these six patients should also be noted (Table 4).

The results of the quantitative neurological and speech examinations are shown in Table 5. Patient 38 is not included because of her different status. Of the four patients scored for neurological status at the beginning and at the end of the 8-week tetrathiomolybdate treatment, two showed mild improvement and two were unchanged. Of the five patients scored for dysarthria, two showed mild improvement and three were unchanged. The most important finding is that none worsened.

A patient deserving of special comment is patient 68. This patient had the most severe brain involvement detected by magnetic resonance imaging of the brain of any of our series of 61 patients. He had involvement of white matter areas as well as basal ganglia. This patient's course was similar to the other patients in that his neurological symptoms referable to Wilson's disease did not worsen. It was different in that his recovery was much less complete and that intermittent seizures developed. We do not believe the seizures are related to therapy with tetrathiomolybdate, but they are probably due to the original brain damage. The only other patient in our series who had white matter lesions observed on magnetic resonance imaging scans also had seizures, and he had been treated only with penicillamine.

COMMENT

Two aspects of the results reported here on the first six patients treated with tetrathiomolybdate will be discussed. The first aspect is an analysis of the preliminary results related to the drug and drug regimen—drug stability, methods of storage, methods of assay, methods of administration, dose response, methods of evaluating end points of therapy in this setting, and methods of transition to maintenance anticopper agents. The second aspect relates to the therapeutic objective of quickly gaining control over copper toxicity and preventing neurological worsening.

Addressing the first aspect, we believe that we have evolved preliminary methodology that makes tetrathiomolybdate operationally quite usable. The active product is easily assayed, and we have a biological assay that confirms potency. The drug in bulk form stored under anaerobic conditions at room temperature is adequately stable. Under conditions of use by patients for 8 weeks it is also adequately stable.

The therapeutic end points of interest with respect to copper were blockade of intestinal copper absorption and neutralization of potentially toxic levels of copper. We found that these end points could be effectively evaluated by using copper balance and blockade of copper 64 absorption for the first end

Table 3.—Response of Liver-Derived Serum Enzyme Values in Patient 38

Serum Enzyme	Normal Value, U/L	Baseline, U/L	Day of Tetrathiomolybdate Therapy, U/L 5	7	12	13	14	19	21
Aspartate aminotransferase	2-35	70	46	42	41	49	47	34	35
Alanine aminotransferase	2-35	166	67	70	72	75	66	58	65
Lactic dehydrogenase	60-200	234	191	161	155	210	151	140	147
Alkaline phosphatase	30-130	141	132	138	129	138	114	112	108

Table 4.—Response of Copper Values in Urine to Therapy*

Patient No.	24-Hour Values (Trichloroacetic Acid Soluble), μmol/d Baseline	End of Tetrathiomolybdate Therapy
56	3.4	2.5
61	2.1	1.8
63	3.4	1.4
68	5.0	1.3
79	5.2	4.2
38	7.6	4.8
Mean ± SD	4.5 ± 1.9	2.6 ± 1.5

*$t = 3.47$; $P < .02$.

Table 5.—Neurological and Speech Evaluation*

Patient No.	Quantitative Neurological Rating Initial	End	Interpretation	Dysarthria Rating Initial	End	Interpretation
56	20	17	Improved	5.5	4.5	Improved
61	31	24	Improved	6	6	Unchanged
63	21.5	21	Unchanged	4.5	3	Improved
68	37	. . . †	. . .	5	4.5	Unchanged
79	15	14.5	Unchanged	2	2	Unchanged

*From Young et al.[12]

†This patient's results were not scorable at the time of the neurological examination because of sedation from antiseizure medication.

point of interest, and the ratio of molybdenum to NCPCu in plasma for the second. The latter determination can be used to titrate the time point at which the NCPCu is fully occupied with tetrathiomolybdate. We found the use of trichloroacetic acid copper solubility[6,9] less reliable, particularly if the patient had had a significant amount of circulating ceruloplasmin.

It appears that to obtain both mechanisms of action a program of administering the drug both *with* (to obtain blockade of copper absorption) and *between* meals (to obtain tetrathiomolybdate absorption and neutralization of potentially toxic levels of copper) is optimal. It appears that a daily dose of 2 to 3 mg/kg of body weight, with a distribution of drug approximately one third with meals and two thirds between meals, achieves both effects. Blockade of copper absorption is immediate, while it took 8 to 29 days (mean, 16.7 days) to accomplish complete neutralization of NCPCu in plasma.

We evaluated only one type of transition to maintenance therapy, that to zinc acetate. This transition went smoothly. Based on unpublished animal studies, we also believe that a patient's therapy could be transitioned to penicillamine or trien without difficulty.

With regard to the second aspect, whether tetrathiomolybdate is superior to other agents in the initial treatment of Wilson's disease in terms of preventing worsening of neurological disease, obviously a more definitive study, possibly a side-by-side comparison, must be performed. The post hoc penicillamine study revealed that the condition of 13 of 25 patients worsened,[3] and, in the present study with tetrathiomolybdate, the condition of zero of five patients worsened (patient 38 cannot be counted because her situation was not one of initial treatment). While these results are statistically significant by χ^2 analysis ($P < .05$), they must be taken as only giving preliminary encouragement until a more definitive study is conducted. In spite of the limited number of patients studied, we believe these early results with tetrathiomolybdate are quite exciting. From the theoretical standpoint, tetrathiomolybdate has ideal properties for quickly controlling copper toxicity, and these early results so far bear out the theoretical expectation. No toxic reactions were observed from this therapy over the 8 weeks of use in these patients.

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References

1. Brewer GJ, Yuzbasiyan-Gurkan V. Wilson's disease: an update with emphasis on new approaches to treatment. *Dig Dis.* 1989;7:178-193.
2. Brewer GJ, Yuzbasiyan-Gurkan V, Young AB. Treatment of Wilson's disease. *Semin Neurol.* 1987;7:209-220.
3. Brewer GJ, Terry CA, Aisen AM, et al. Worsening of neurological syndrome in patients with Wilson's disease with initial penicillamine therapy. *Arch Neurol.* 1987;44:490-494.
4. Brewer GJ, Hill GM, Prasad AS, et al. Oral zinc therapy for Wilson's disease. *Ann Intern Med.* 1983;99:314-320.
5. Hill GM, Brewer GJ, Prasad AS, et al. Treatment of Wilson's disease with zinc, I: oral zinc therapy regimens. *Hepatology.* 1987;7:522-528.
6. Mills CF, El-Gallad TT, Bremner I. Effects of molybdate, sulfide, and tetrathiomolybdate on copper metabolism in rats. *J Inorgan Biochem.* 1981;14:189.
7. Bremner I, Mills CF, Young BW. Copper metabolism in rats given di- or trithiomolybdates. *J Inorgan Biochem.* 1982;16:109.
8. Mills CG, El-Gallad TT, Bremner I, et al. Copper and molybdenum absorption by rats given ammonium tetrathiomolybdate. *J Inorgan Biochem.* 1981;14:163.
9. Gooneratne SR, Howell JM, Gawthorne JM. An investigation of the effects of intravenous administration of thiomolybdate on copper metabolism in chronic Cu-poisoned sheep. *Br J Nutr.* 1981;46:469.
10. McDonald JW, Friesen GD, Rosenhein LD, et al. Syntheses and characterization of ammonium and tetraalkylammonium thiomolybdates and thiotungstates. *Inorgan Chim Acta.* 1983;72:205-210.
11. Hill GM, Brewer GJ, Juni JE, et al. Treatment of Wilson's disease with zinc, II: validation of oral ^{64}copper uptake with copper balance. *Am J Med Sci.* 1986;12:344-349.
12. Young AB, Shoulson I, Penney JB, et al. Huntington's disease in Venezuela: neurologic features and functional decline. *Neurology.* 1986;36:244-249.
13. Darley FL, Aronson AE, Brown JR. *Motor-speech Disorders.* Philadelphia, Pa: WB Saunders Co; 1975.

The Neural Substrate of Memory Impairment Demonstrated by the Intracarotid Amobarbital Procedure

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Robert A. Novelly, PhD; Dennis D. Spencer, MD; Jung H. Kim, MD

• The intracarotid amobarbital sodium (Amytal) procedure (IAP) was performed for 46 patients with temporal lobe epilepsy (21 with left seizure foci; 25 with right seizure foci). After anteromedial temporal lobectomy, neuronal densities were established for hippocampal subfields CA1, CA2, and CA3; the hilum; and the dentate granule cell layer. Intracarotid amobarbital procedure memory results were related to CA3 neuronal loss only. Patients who did not demonstrate memory after injection contralateral to the seizure focus had significantly fewer cells in CA3 than patients who did. Additionally, a significant correlation was observed between the intracarotid amobarbital procedure memory examination raw score after injection contralateral to the seizure focus and CA3 cell density. Using χ^2 analysis, significant differences were documented in the frequency with which memory was demonstrated after injection contralateral to the seizure focus for groups of patients classified by degree of CA3 neuronal loss. This finding supports prior research showing subfield specificity in some memory processes.

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The intracarotid amobarbital sodium (Amytal) procedure (IAP) originally involved only the assessment of language during unilateral anesthetization. A brief memory assessment was added to the IAP[1] as a means of avoiding the amnesic syndrome that occasionally followed unilateral temporal lobectomy with hippocampectomy.[2] Although IAP memory findings are considered by many to be a measure of hippocampal function,[3-6] few attempts have been made to demonstrate the correspondence of IAP memory findings and hippocampal damage.

Rausch et al[6] found that patients with severe neuron loss throughout the hippocampus generally failed the IAP memory examination, but results in patients with moderate neuron loss were mixed. These authors did not examine the hippocampal subfields individually. Sass et al[7] demonstrated a relationship between clinical memory impairment and neuron loss only in CA3 and the hilar area. Rausch and coworkers' use of a composite measure of neuron loss may have obscured the relationship between IAP memory performance and neuron loss in specific subfields for those patients with only moderate hippocampal damage. The present report summarizes evidence of specificity in the relationship between hippocampal neuron loss and IAP memory performance.

PATIENTS AND METHODS

Patients

Forty-six patients with medically refractory epilepsy localized to the temporal lobe (21, to the left; 25, to the right) underwent the IAP prior to surgery. Seizure onset was localized using electroencephalography of the scalp with simultaneous audiovisual recording of at least three clinical seizures. In addition, 35 patients underwent invasive electroencephalographic evaluation (12 had depth electrodes, one had subdural electrodes, and 22 had both depth and subdural electrodes implanted). Computed tomography, magnetic resonance imaging, and angiography detected no structural lesions (eg, tumors, vascular malformations, and infarcts). Mesial temporal sclerosis was not considered a structural lesion for purposes of this study.

All patients were 16 years of age or older and left hemisphere dominant for speech. Every patient had a full-scale intelligence quotient above 70, as measured by the Wechsler Adult Intelligence Scale-Revised. Patients with left seizure foci did not differ significantly from patients with right seizure foci with regard to history of febrile convulsions, age of seizure intractability, or age at surgery. This information is summarized in Table 1. Excluding seizures during the acute postoperative period and those occurring with medication changes, 40 patients were seizure free during the 6-month period following surgery. The remaining six patients (four with left foci, two with right foci) had at least an 80% reduction in seizure frequency.

IAP

Patients were seizure free for at least 12 hours before the IAP was performed. Both hemispheres were studied in all patients, and the hemisphere with the suspected lesion was always injected with amobarbital first. The period between injections was approximately 1 hour in duration. Prior to the procedure, a brief language examination was performed to detect any preexisting language disorder. This language examination assessed expository speech, comprehension, repetition, and naming.

Catheterization of the internal carotid artery was achieved via a transfemoral approach. One hundred thirty milligrams of 10% amobarbital sodium, diluted in 100 mL of saline was injected manually. The duration of the injection was approximately

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4 seconds. When dense hemiplegia contralateral to the injection side was demonstrated, memory stimuli were presented visually to the patient. The stimuli were similar in design for both hemispheres. These stimuli included two line drawings of common objects, two simple words, a colored geometric form, and a simple arithmetic operation. Patients were asked to name the objects, to read the words, to identify the color and shape of the geometric form, and to recite the arithmetic problem. When the dominant hemisphere was injected, the patient could not comply with these commands, because he or she could not speak. However, the patient's attention to stimuli could be demonstrated by accurate visual tracking when the stimuli were slowly moved. Each stimulus was exposed for approximately 25 seconds, only during the period of acute anesthetization.

Identification of the memory stimuli during anesthetization constituted a portion of the language examination (ie, object naming and reading). After the memory stimuli were presented, examination of spontaneous speech, repetition, and comprehension continued. Approximately 10 minutes after the injection, if normal strength was demonstrated bilaterally and no aphasic signs were present, the patient was asked to recall the memory stimuli. For those items that were not recalled spontaneously, recognition was tested by asking the patient to select from four stimuli (one correct item and three foils) the one that had been exposed during the procedure. The patient's test score was the sum of items recalled and recognized. Ordinarily, test scores of 2 or more (ie, at least 33% correct responses) were considered to reflect intact memory. However, to approximate the procedure used elsewhere,[6] IAP memory results were also computed, with 4 points (ie, 67% correct responses) required for a passing score.

All IAP memory results presented in this report refer to performance following injection of the hemisphere contralateral to the seizure focus. In other words, the results refer to performance by the hemisphere ipsilateral to the seizure focus, where the operation would ultimately be performed. All patients demonstrated memory following injection of the hemisphere ipsilateral to the seizure focus, which is required for patients undergoing temporal lobectomy at our institution.

Surgical Procedure and Tissue Analysis

The surgical procedure and the method of tissue analysis used in this study were identical to those detailed in a previous publication.[7] For the convenience of the reader, these procedures are reviewed here as well.

All patients underwent anteromedial temporal lobectomy and radical hippocampectomy, without intraoperative cortical stimulation or electrocorticography. The anteromedial temporal lobectomy involved small neocortical resection (3 to 3.5 cm for the dominant hemisphere, 4 to 4.5 cm for the nondominant hemisphere). The cortical incision bisected the middle temporal gyrus, sparing the superior temporal gyrus.

Table 1.—Demographic Information*

	Seizure Foci	
	Left	Right
Group size	21	25
Febrile convulsions	14	16
Age at intractability, y	12.5	10.8
Age at surgery, y	29.5	30.2
Verbal IQ	91.3	96.1
Performance IQ	94.9	96.0

*IQ indicates intelligence quotient.

Table 2.—Correlation of Intracarotid Amobarbital Procedure Memory Results and Pyramidal Cell Density

	CA1	CA2	CA3	Hilar Area	Granule Area
r	.17	.25	.38*	.12	.13
No.	46	39	43	46	45

*$P < .01$.

The hippocampus was exposed by dissection of the occipitotemporal fasciculus. Medial structures, including the amygdala, parahippocampus, and hippocampal formation, were removed en bloc, using the operating microscope. The hippocampus was cut posteriorly at its curve around the superior colliculus.

A coronal section, 2 mm in thickness, was obtained from the midsection of the hippocampus. This was placed in 4% buffered formaldehyde solution in the operating room, and then transferred to the laboratory for further fixation, dehydration, and paraffin embedding. Four paraffin sections, 6 μm in thickness, were stained with hematoxylin-eosin, Luxol fast blue, and Nissl and/or Bodian method. However, the most successful results were obtained using hematoxylin-eosin, and the majority of cases were processed in this fashion.

Separate cell counts were obtained for CA1, CA2, CA3, the hilar area, and the granular layer of area dentata. Neuronal nuclei were counted in areas measuring 200 × 400 μm for the pyramidal cell fields and 50 × 100 μm for the granule cell area. The neuronal counts were adjusted using Abercrombie's formula (8 μm was used for the nuclear diameter of pyramidal cells; and 6 mm, for granular neurons).[8] Five separate areas were counted for each subfield, and the average for each subfield was computed. Separate counts were obtained from two observers who were blind with respect to presurgical examination findings. Neuronal densities are expressed as measures of volume (mean cell count per cubic millimeter).

Normative cell densities were established using tissue collected during autopsy of 14 adults who died of nonneurologic causes. Tissue was obtained within 8 hours post mortem.

RESULTS

Patients with epilepsy, contrasted with autopsy controls, had significant pyramidal cell loss in CA1, CA2, CA3, and the hilum of area dentata (multivariate analysis of variance results, $P < .001$). Granule cell densities within area dentata also were significantly less than those of the autopsy controls ($P < .001$). Neuron densities of patients whose seizure focus was identified by nonsurgical means (ie, electroencephalography of the scalp, neuropsychological examination, and IAP findings) did not differ significantly from those of patients who underwent depth electrode implantation or subdural electroencephalographic recording.

Table 3.—Cross Tabulation of Intracarotid Amobarbital Procedure Memory Failures and Classification of CA3 Neuron Loss (N = 43)

	Standard Scoring Criterion	
	Fail	Pass
Severe neuron loss	9	3
Moderate neuron loss	9	18
Normal cell counts	1	3

Table 4.—Cross Tabulation of Intracarotid Amobarbital Procedure Memory Failures and Classification of CA3 Neuron Loss (N = 43)

	Conservative Scoring Criterion	
	Fail	Pass
Severe neuron loss	12	0
Moderate neuron loss	19	8
Normal cell counts	1	3

The mean number of items recalled by patients with left temporal seizure foci following perfusion of the right hemisphere was 2.29 items (SD, 2.22 items). Patients with right temporal seizure foci recalled an average of 1.96 items (SD, 2.01 items) following perfusion of the left hemisphere. The group difference was not statistically significant; therefore, lateralization of the seizure foci was not considered in subsequent analyses.

Patients were classified by their success or failure in demonstrating memory within the hemisphere in which surgery would ultimately be performed. Using our standard scoring criterion (pass, 2 or more points), 25 patients demonstrated memory following injection contralateral to the planned surgery site (ie, a pass) and 21 did not (ie, a failure). Using the alternative scoring criterion (pass, 4 or more points), 11 patients passed and 35 failed.

Patients who failed the IAP memory examination had significantly fewer neurons in CA3 ($P < .01$) than patients who passed the examination, regardless of the scoring criterion (eg, 2 points or 4 points). Pearson product moment correlations documented a statistically significant correlation between IAP memory examination raw scores (range, 0 to 6) and CA3 volumetric cell density ($r = .38$; $P < .01$) (Table 2). No other statistically significant correlations or group differences were observed for any other hippocampal subfield.

Patients were divided into three groups using methodology similar to that of Rausch et al.[6] Rausch and colleagues separated patients with less than 20% of the mean volumetric neuron measurement of the autopsy controls from those patients with less severe neuron loss. Patients in the present sample who had severe hippocampal neuron loss also were separated from the others. The classification was based only on the number of neurons in CA3, the only field in which neuron counts were related to IAP memory performance. The autopsy controls in Rausch and coworkers' study had a mean volumetric neuron density of 21773 in CA3. Rausch et al[6] and Babb et al[9] used the same normal controls. Rausch and associates established a criterion for the classification of severe neuron loss (80% the number of cells in autopsy controls reported by Babb and colleagues). However, they did not establish a normal range. For consistency in classification of patients with severe neuron loss, we used the same criterion that they did. In the absence of any standard proposed by Rausch and coworkers, we established a normal range using our own autopsy controls. Patients in our sample whose volumetric neuron density was less than 4354.6 for CA3 (20% of 21773) were classified as having severe neuron loss (n = 12).

Rausch et al[6] considered all other patients (ie, those with less than 80% neuron loss) to have moderate neuron loss. Inspection of our data indicated that some patients had minimal or no neuron loss. Therefore, a third group was identified. Patients whose neuron counts were within two standard deviations of mean volumetric neuron density observed for our autopsy control sample were classified as having normal neuron counts (n = 4). All others were classified as having moderate neuron loss (n = 27). The tissue samples for three patients were not suitable for establishing the volumetric cell density of CA3. Therefore, only 43 of 46 patients were classified according to CA3 neuron loss.

The IAP memory findings (pass or fail) for the side that was operated on were cross tabulated with neuron density classifications (ie, severe neuron loss, moderate neuron loss, and normal). These cross tabulations are shown in Tables 3 (pass, 2 items or more) and 4 (pass, 4 items or more). Failures during the IAP memory examination were increasingly more frequent with greater neuron loss. The χ^2 analysis was statistically significant, regardless of the scoring criterion ($P < .05$).

COMMENT

In 1958, Penfield and Milner[10] reported two cases of persistent anterograde amnesia following unilateral temporal lobectomy with hippocampectomy. These two cases of amnesia were quantitatively similar to the syndrome observed following bilateral hippocampectomy,[11] so Penfield and Milner suspected the presence of a lesion in the temporal lobe contralateral to the surgical procedure. Hippocampal injury contralateral to the surgical excision was ultimately demonstrated at autopsy.[10] Later, Milner et al[1] reported "a severe and lasting memory disturbance" following unilateral temporal lobectomy with hippocampectomy in three of 18 patients with bilateral electroencephalographic or radiological evidence of damage to the temporal lobes.

Milner et al[1] proposed that severe postoperative memory impairments following unilateral temporal lobectomy with hippocampectomy could be avoided by a technique that accurately assessed the integrity of each hippocampal formation. At the time, the IAP was becoming accepted as a reliable technique for determining speech lateralization. Milner and coworkers hypothesized that when the hemisphere that had been selected for surgery was temporarily anesthetized with amobarbital sodium, memory examination would identify "a lesion involving the hippocampal zone of the opposite hemisphere." Consequently, they added a brief memory assessment to the IAP.

Initially, Milner et al[1] encountered failures on the IAP memory test only after injection contralateral to the side of the proposed surgery (ie, when the side of the suspected lesion was examined). These cases posed no risk for postoperative amnesia, because adequate memory function was present in the contralateral hemisphere. Later, Milner[3] encountered memory impairments after injection of the hemisphere ipsilateral to the proposed surgery. When this result was obtained the patient was not denied surgery Instead, the surgical procedure fo these patients was modified to spar the hippocampus and parahippocam pal gyrus, based on the belief that IA memory failure indicated a damage hippocampus contralateral to the injection side.[3,5] Milner[3] reported thre cases in which a patient, having faile to demonstrate adequate memory o the side contralateral to the propose surgery, underwent temporal lobectomy in which the hippocampus wa spared. None of the patients involve became amnesic.

In the years since its development the IAP memory examination has become a routine component of the presurgical evaluation of patients wit medically refractory epilepsy.[11] Lik Milner,[1,3] many researchers believe th IAP is a measure of medial tempora lobe or, specifically, of hippocampa function. This interpretation is sometimes stated explicitly.[1-3,6] In other reports, the connection between IA memory performance and hippocampal functioning can be inferred fro the practice of preserving the hippocampus during surgery for patients who failed to demonstrate memory contralateral to the surgical site (ie when the ipsilateral hemisphere was perfused).[12]

Several studies have shown that the likelihood of IAP memory failure is greater when the hemisphere contralateral to the seizure focus is perfused.[1,6,13,14] However, there has been little direct evidence that the IAP is sensitive to the degree of hippocampal damage.

Rausch et al[6] examined the memory of 30 patients during the IAP. Quantified pyramidal cell counts for the subfields of the hippocampus and the prosubiculum were obtained for 29 of the 30 patients following unilateral temporal lobectomy and hippocampectomy. Neuron densities were established for anterior and posterior planes, the latter defined as 3 cm from the anterior aspect of the hippocampus. Four of five patients with severe hippocampal damage, operationally defined as more than 80% neuron loss, failed to demonstrate memory from the hemisphere selected for surgery (ie, following perfusion of the hemisphere contralateral to the seizure focus). In contrast, only 58% of patients with moderate neuron loss failed to demonstrate memory during the IAP. Rausch et al[6] noted that, "Several patients with minimal hippocampal damage failed IAP memory testing on contralateral injection, while patients with more marked damage passed the IAP memory component." The authors concluded that IAP memory failure in patients with severe hippocampal damage was the result of the neuron loss. They suggested that IAP memory failures by patients with moderate neuron loss could have involved recent seizure phenomena or interictal epileptiform activity. Nevertheless, they regard all IAP memory failures as "indicative of significant surgical risk to global memory."

The present study was designed to further examine the sensitivity of the IAP memory examination to hippocampal neuron loss. Rausch and colleagues'[6] measure of hippocampal neuron loss was a composite of five fields. A previous report of the relationship between hippocampal neuron loss and clinical memory indicated that only neuron loss in CA3 and the hilum correlated with memory impairment.[7] The present study was designed to determine whether hippocampal subfield specificity exists with respect to the IAP memory findings.

Patient selection criteria for the present study were virtually identical to those of Rausch et al.[6] In both samples, localization of seizure onset rather than interictal spiking was the criterion for surgical planning. A comparable number of patients in each study were selected by depth electrode implantation, subdural recordings, and surface recording only. The patients were approximately the same age when habitual seizures began and at surgery. The rate of failures on the IAP memory examination was similar. Rausch and associates reported failures in 19 (66%) of 29 patients. Using their scoring criterion, we observed memory failures in a comparable number of patients (35 [76%] of 46). Surgical techniques were similar, except that the procedure described herein resulted in a more radical excision of the hippocampus. Even so, the section obtained for analysis in this study corresponded to the posterior section obtained by Rausch et al.[6]

In the present sample, IAP memory results were related to neuron loss only in CA3. This relationship was demonstrated in three ways. Patients failing the IAP had significantly fewer neurons in CA3 than patients who had passed, regardless of the scoring criterion (eg, 2 or 4 items required for a passing score). A significant correlation was observed between IAP memory examination raw score and CA3 neuron density. χ^2 Analyses documented differences in the frequency of IAP memory failures, regardless of scoring criterion, in groups of patients classified according to the degree of neuron loss in CA3.

By classifying patients only according to neuron loss in CA3, we identified a greater number of patients with severe neuron loss (12 [28%] of 43). Only five (17%) of 29 patients in the study of Rausch et al[6] were classified as having severe neuron loss using the composite index. Patients with severe neuron loss could reasonably have been expected to fail the IAP memory examination. Four of the five patients in Rausch and coworkers' sample and all 12 of the patients in our sample did so (using Rausch and coworkers' scoring criterion). By classifying patients only by neuron loss in CA3, we also identified four patients (9%) with normal cell counts. These four patients could reasonably have been expected to pass the IAP memory examination, and three of them did. Altogether, classifying patients only on the basis of neuron loss in CA3 allowed us to make reasonable predictions regarding IAP memory performance for 37% of our sample (16 of 43 patients), and 94% of these (15 of 16) performed as expected. In contrast, Rausch and colleagues' classification system identified only 17% of the sample about whom reasonable predictions could be made, and only 80% of these performed as expected.

The findings of the present study and the contrast of this study with that of Rausch et al[6] suggest that specificity with regard to subfield exists in the relationship of IAP memory performance and hippocampal neuron loss. This finding is consistent with that of a prior study showing similar specificity in the relationship of clinical memory (eg, list learning) and hippocampal neuron loss.[7] Sass et al[7] reported that performance on the verbal Selective Reminding Test correlated only with CA3 and hilar neuron loss in patients with left temporal seizure foci.

Like Rausch et al,[6] we observed mixed results in patients with moderate neuron loss. Rausch and associates reported that 14 (58%) of 24 patients with moderate neuron loss failed to demonstrate memory during the IAP. Several explanations for these failures were offered. These included recent seizure phenomena or interictal epileptiform activity; the role of the hippocampal lesion was minimized. Rausch and coworkers appeared to interpret IAP memory failures in the moderate neuron loss group as false-positive errors (with respect to documenting severe neuron loss). Using their scoring criterion, 19 (70%) of 27 patients in our sample with moderate neuron loss in CA3 failed the IAP memory examination. We believe the hippocampal lesion was central to these failures. Therefore, we are inclined to interpret adequate demonstration of memory during the IAP by patients with moderate neuron loss as false-negative errors (with respect to documenting the neuron loss in CA3).

There can be several reasons why moderate neuron loss in CA3 may be associated with intact memory during the IAP. Rausch et al[6] reported a relationship between perfusion of the posterior circulation and IAP failure for a portion of their sample (ie, those with severe neuron loss). The cerebral vasculature also varies with regard to filling of the anterior cerebral distribution from a middle cerebral injection. The reappearance of contralateral motor function or speech is used as an index of hemispheric recovery from anesthetization. Variance in vascular distribution of the frontal areas, as well as variance in the threshold for anesthetization and rate of recovery of frontal vs medial temporal areas, may lead to participation of the injected hemisphere in the mnemonic process, despite the presence of contralateral hemiplegia or mutism/dysphasia. Finally, recognition memory is tested in a multiple choice format. With a ratio of 3:1 (foils to targets), chance responding would yield an average score of 1.67 correct. The possibility that some patients correctly guessed one or more stimuli must be considered. We minimize this by scoring items as correct only if the patient reports a clear recognition of the item (ie, he or she is not guessing). However, it is impossible to control completely for guessing.

The overwhelming majority of patients in our sample failed to demonstrate memory from the side of seizure focus (ie, after perfusion of the hemisphere contralateral to the seizure focus) during the IAP memory examination (using the scoring criterion of Rausch et al[6]). All but one of the patients who failed the IAP memory examination had moderate or severe neuron loss in CA3. Furthermore, a significant relationship between moderate or severe neuron loss in CA3 and clinical memory has also been demonstrated.[7] The results of the present study indicate that failure to demonstrate memory following anesthetization of the hemisphere that will be operated on identifies patients at risk for significant postoperative memory impairments. These data support the practice of denying surgery to patients who fail to demonstrate memory during the IAP from the hemisphere that will remain intact after the planned surgery.

These findings and those of Sass et al[7] demonstrate a relationship between damage in CA3 and some types of memory impairments. Although noting this correlation, we do not ascribe to CA3 a special role with regard to some specific aspect of memory. Neuroanatomical studies have shown CA3 to be part of a neural network that includes CA1 and the subiculum.[15-17] Zola-Morgan et al[18] reported memory impairments in a patient with bilateral CA1 lesions. Jarrard et al[19,20] reported that damage to the subiculum had a causative role with regard to some memory impairments in animals. Although it is premature to specify the manner in which damage to any of these areas affects memory, we believe there is ample evidence to suggest that hippocampal subfield specificity exists with regard to cognitive functions.[17] We encourage future researchers to further investigate hippocampal subfield specificity, rather than to assume that the hippocampus functions as a single unit.

References

1. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium Amytal. *Trans Am Neurol Assoc.* 1962;87:224-226.
2. Penfield W, Mathieson G. An autopsy and a discussion of the role of the hippocampus in experiential recall. *Arch Neurol.* 1974;31:145-154.
3. Milner B. Disorders of learning and memory after temporal lobe lesions in man. *Clin Neurosurg.* 1972;19:421-446.
4. Blume WT, Gabow JD, Darley FL, Aronson AE. Intracarotid amobarbital test of language and memory before temporal lobectomy for seizure control. *Neurology.* 1973;23:812-819.
5. Jones-Gotman M. Commentary: psychological evaluation—testing hippocampal function. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:203-211.
6. Rausch R, Babb TL, Engel J Jr, Crandall PH. Memory following intracarotid amobarbital injection contralateral to hippocampal damage. *Arch Neurol.* 1989;46:783-788.
7. Sass KJ, Spencer DD, Kim JH, Westerveld M, Novelly RA, Lencz T. Verbal memory impairment correlates with hippocampal pyramidal cell density. *Neurology.* 1990;40:1694-1697.
8. Abercrombie M. Estimation of nuclear population from microtome sections. *Anat Rec.* 1946; 94:239-247.
9. Babb TL, Brown WJ, Pretorius J, Davenport C, Lieb JP, Crandall PH. Temporal lobe volumetric cell densities in temporal lobe epilepsy. *Epilepsia.* 1984;25:729-740.
10. Penfield W, Milner B. Memory deficit produced by bilateral lesions in the hippocampal zone. *Arch Neurol Psychiatry.* 1958;79:475-497.
11. Rausch R. Psychological evaluation. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:181-195.
12. Ojemann GA, Dodrill CB. Verbal memory deficits after left temporal lobectomy for epilepsy: mechanism and intraoperative prediction. *J Neurosurg.* 1985;62:101-107.
13. Engel J Jr, Rausch R, Lieb JP, Kuhl DE, Crandall PH. Correlation of criteria used for localizing epileptic foci in patients considered for surgical therapy of epilepsy. *Ann Neurol.* 1981; 9:215-224.
14. Milner B. Psychological aspects of focal epilepsy and its neurosurgical management. *Adv Neurol.* 1975;8:299-321.
15. Swanson LW, Cowan WM. An autoradiographic study of the organization of the efferent connections of the hippocampal formation in the rat. *J Comp Neurol.* 1977;172:49-84.
16. Swanson LW, Wyss JM, Cowan WM. An autoradiographic study of the organization of intrahippocampal association pathways in the rat. *J Comp Neurol.* 1978;181:681-715.
17. Lynch G, Baudry M. Structure-function relationships in the organization of memory. In: Gazzaniga MS, ed. *Perspectives in Memory Research.* Cambridge, Mass: MIT Press; 1988:23-91.
18. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci.* 1986;6:2950-2967.
19. Jarrard LE. Selective hippocampal lesions and behavior: effects of kainic acid lesions on performance of place and cue tasks. *Behav Neurosci.* 1983;97:873-889.
20. Jarrard LE, Feldon J, Rawlins JNP, Sinden JD, Gray JA. The effects of intrahippocampal ibotenate on resistance to extinction after continuous or partial reinforcement. *Exp Brain Res.* 1986;61:519-530.

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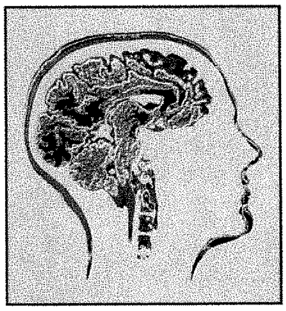

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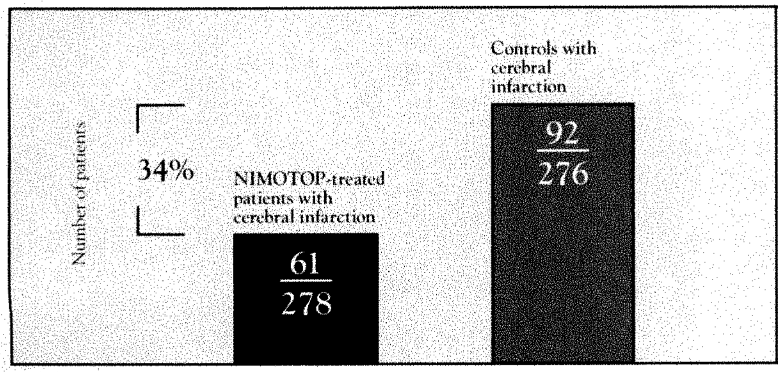

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Lazarewicz JW, et al. *Stroke* 1989.

"[In humans] The data thus suggest that nimodipine neither prevents nor reverses cerebral vasospasm. Calcium channel blockers such as nimodipine may have an effect on cerebral arterioles that are below the limits of resolution of angiography. . . ."[1]

Pickard JD, et al. *Br Med J* 1989.

Please see references and Brief Summary of full prescribing information on next page.

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CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479**
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/k q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions o calcium channel blockers. It must be noted, however, that SAH is frequently accompanied b alterations in consciousness which lead to an under reporting of adverse experiences. Patient who received nimodipine in clinical trials for other indications reported flushing (2.1%) headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet count (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

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Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

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If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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REFERENCES

1. Pickard JD, Murray GD, Illingworth R, et al. *Br Med J.* 1989;298:636-642. **2.** Solomon RA, Fink ME. *Arch Neurol.* 1987;44:769-773. **3.** Petruk KC, West M, Mohr G, et al. *J Neurosurg.* 1988;68:505-517. **4.** Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. *Acta Neurol Scand.* 1987;76:267-271. **5.** Scriabine A, van den Kerckhoff W. Ann NY *Acad Sci.* 1988;522:698-706. **6.** Lazarewicz JW, Pluta R, Salinska E, Puka M. *Stroke.* 1989;20:70-77.

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Dominant-Side Intracarotid Amobarbital Spares Comprehension of Word Meaning

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• Abolition of speech production after intracarotid amobarbital injection is generally considered evidence for language laterality. However, complex auditory comprehension may be preserved after injection of the dominant (left) side. The possibility that this sparing may be due to the intracarotid amobarbital injection not adequately deactivating some of the areas responsible for speech comprehension in the posterior part of the hemisphere was tested with a task known to be critically dependent on the left posterotemporal-inferoparietal region, one assessing visuoverbal semantic relatedness. Even when the intracarotid injection of the left side produced marked deficits of speech production, comprehension of semantic relations was still intact in eight of 15 patients. Ten of these 15 patients also received right carotid injections, none of which affected comprehension of semantic relatedness. These data indicate that the intracarotid amobarbital injection cannot always specify the laterality of all language functions, an important concern when considering surgical procedures in the dominant posterotemporal-inferoparietal region.

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The intracarotid amobarbital test has been used extensively as one probe of cerebral lateralization of language and memory.[1-6] Its use for this purpose is based on three assumptions. The first is that amobarbital in sufficient quantity will functionally deactivate the regions through which it flows. The second is that carotid injection of amobarbital can reach all brain areas of one hemisphere that are involved in language. The third is that there is no substitution for these language functions by either ipsilateral or contralateral hemispheric regions, at least over the short interval of the test.

These assumptions may not all be correct, as some results obtained with this technique have been difficult to reconcile with other results obtained similarly. For example, left (dominant) intracarotid amobarbital injection will suppress speech production[2] and impair comprehension of commands to point to simple shapes,[7] yet spare comprehension of commands to move body parts.[2] Such findings suggest that language impairment during Wada[1] testing cannot be viewed as an all-or-nothing phenomenon.

We propose that some important language comprehension functions of the left hemisphere may not be affected by left intracarotid amobarbital injection, in particular, those critically dependent on the left posterotemporal-inferoparietal region.[8,9] To test this hypothesis, we studied performance on a task known to be specifically sensitive to damage in these regions, the ability to comprehend the semantic relatedness between a picture and a word,[9] and compared performance on this task with the ability to name and read orally the individual items during the interval of amobarbital action.

PATIENTS AND METHODS

Patients

Data from 15 patients were selected from those of 22 consecutive patients studied during a 10-month interval. All examinations were performed as part of the clinical examination of medically intractable epilepsy. All patients gave informed consent after the nature of the procedure was fully explained. The 15 patients selected for this study met the following criteria: (1) normal language and neuropsychologic abilities on baseline clinical testing, (2) either left-sided or bilateral injections, (3) absence of significant cross-over of dye to the contralateral hemisphere during the angiogram, and (4) completion of the clinical protocol to be described. Patient profiles are summarized in Table 1.

Procedures

For the intracarotid amobarbital injection, the internal carotid artery was catheterized transfemorally. Digital subtraction angiography or cut-film angiography was then performed, using pressure injection. Following the angiogram, a 5F catheter was positioned under fluoroscopic guidance in the internal carotid artery at the level of the C-2 vertebra. Amobarbital (125 mg in 1 mL of warmed sterile water) was given through the catheter by hand injection over the course of 2 to 3 seconds, as previously described.[2-6,10] The patient's clinical status was monitored with strength testing of the arms intermittently and with continuous 10-channel electroencephalogram (EEG) recording, using a modified longitudinal bipolar montage (except for one patient who had a transverse montage). The derivation used was the following: F_{p1}-F_7, F_7-T_3, T_3-T_5, $F_{p2}F_8$, F_8-T_4, T_4-T_6, F_3-C_3, C_3-P_3, F_4-C_4, and C_4-P_4.

Language and memory testing was begun using a standard protocol when adequate hemispheric deactivation was attained unilaterally, as determined by flaccid paralysis contralaterally and anterior EEG slowing ipsilaterally, and after resolution of any initial period of inattention or confusion. First, six objects were presented visually for naming and remembering,[6] followed by two words for reading, two pictures for naming, the picture-word association task to be described, and further tasks of language and visuospatial function (including oral reading of concrete and abstract words, category membership, property judgment, relative distance discrimination, and imagery tasks). When tested on the picture-word association task, all patients

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Table 1.—Patient Profiles*

Patient No./ Age, y	Handedness	Education, y	Age of Seizure Onset, y	EEG Focus	CT/MRI Structural Lesion	Wada Test,[1] Side of Injection	Side of Language Dominance
1/24	R	12	16	L temporal	L temporal	L	L
2/28	R	12	2	L anterotemporal	...	L	L
3/22	L	12	6	L temporal	...	L	L
4/28	R	19	12	L anterotemporal	...	B	L
5/38	R	17	21	R midtemporal	...	B	L
6/25	R	12	22	L temporal	...	B	L
7/40	R	12	22	L temporal	...	B	L
8/42	L	12	0.5	L temporal	...	B	R
9/17	R	10	14	L midtemporal	L temporoparietal	L	L
10/20	R	12	20	L frontoparietal	L frontoparietal	B	L
11/33	R	18	30	L temporal	...	L	L
12/22	R	14.5	11	R frontal	R frontal	B	M
13/33	R	13	29	L frontotemporal	L frontal	B	L
14/26	R	12	14	L temporal	L temporal	B	L
15/29	R	12	17	R and L temporal	R temporal	B	M

*EEG indicates electroencephalogram; CT, computed tomography; MRI, magnetic resonance imaging; B, bilateral; and M, mixed (dominance).

Table 2.—Summary of Semantic Relatedness, Naming, and Reading Performance on the Picture-Word Association Task, Left Amobarbital Injection*

Patient No.	Semantic Relatedness‡	Naming	Reading
	Intact Group		
1	3/3	0/3	1/3
2	3/3	0/3	1/3
3	4/4	1/4	0/4
4	4/4	1/4	2/4
5	4/4	1/4	0/4
6	4/4	0/4	0/4
7	4/4	0/4	0/4
8†	4/4	4/4	4/4
Total (n = 8)	**30/30**	**7/30**	**8/30**
	Impaired Group		
9	3/4	1/4	0/4
10	3/4	1/4	2/4
11	0/4	0/4	0/4
12	2/4	1/4	1/4
13	2/4	3/4	1/4
14	2/4	0/4	2/4
15	0/4	0/4	0/4
Total (n = 7)	**12/28**	**6/28**	**6/28**

*The fraction represents the number correct divided by the total number of items.

†Patient with crossed language dominance.

‡Overall, performance on the semantic relatedness task was significantly greater than chance ($P < .001$, binomial test).

had, at most, 3/5 strength of the contralateral arm (weak movement against gravity), and all had slowing on the EEG ipsilaterally.

The picture-word association task consisted of a picture (top) and a word (bottom) on a sheet of paper (21.25 × 27.5 cm [8½ × 11 in]). There were four trials, two with semantically associated picture-word pairs (eg, *bed* [picture] and *sleep* [word]), and two with unrelated pairs (eg, *bus* [picture] and *scale* [word]). The patient's task was to name the picture, read the word, and then decide if the two items were related by category or function (semantic-relatedness task). The patients had been trained on these tasks in pretesting, and their training was reinforced by auditory prompting during the test ("Do these go together?" "Are these related?"). Patients responded either orally (yes or no), by nodding or shaking their head, or by performing hand gestures (on which they had been trained previously). Naming the pictures and reading the words used in the task was performed at the same time as semantic relatedness.

All tasks were pretested the day prior to the procedure using stimuli different from those used during the actual test. This pretesting familiarized patients with the procedures and established their baseline levels of performance. Also, patients were warned what to expect in terms of paralysis, disorientation, and inability to speak but not about specific deficits.

RESULTS

For all of the language tests in our standard protocol, all of the patients performed perfectly on pretesting. Performance on language tests (other than the semantic-relatedness task) during the critical phase of the injection clearly distinguished three groups (Table 1): 12 of 15 patients with impaired language during injection of the left side, interpreted as showing left-sided language dominance; two of 15 patients showing language impairment with injection of either carotid artery, interpreted as mixed dominance; and one of 15 patients showing impairment with injection of the right side only, interpreted as right-sided language dominance.

On semantic relatedness, all patients performed perfectly (four of four correct) during pretesting. Therefore, any score less than 100% correct during the injection was considered impaired. Striking dissociations in performance between speech production (naming and reading) and comprehension of the semantic relatedness of the stimulus pairs were noted (Table 2). After injection of amobarbital into the left internal carotid artery 14 of 15 patients had marked impairment on both oral word reading and picture naming, yet 8 (53%) of 15 patients could still determine whether or not the items were related by category or function (Table 2). This percentage is even greater (58%) if the four patients who were left-handed or showed crossed or mixed dominance are excluded.

After injection of amobarbital into the right internal carotid artery, however, semantic relatedness was intact for all patients (Table 3), including the patients with crossed or mixed dominance (patient 8, crossed, and patients 12 and 15, mixed).

We also examined two other possible indexes of amobarbital perfusion of the posterotemporal-inferoparietal region, ie, the arteriographic findings and the EEG. The arteriograms were reviewed by a neuroradiologist (R.N.B.) blinded to the identity of the patients and the results of the study, examining for pattern of vessels and degree of opacification of the posterior cerebral artery. In no patient did the posterior cerebral artery have a direct origin from the anterior circulation. No correlation between the degree of opacification and the pattern of performance was found.

The EEG data were also examined. These data were available in all but three patients (patient 15 had a transverse montage that did not include the T_5 or T_6 electrodes, the data from patient 6 was uninterpretable because of movement artifact, and the data

Table 3.—Summary of Semantic Relatedness, Naming, and Reading Performance on the Picture-Word Association Task, Right Amobarbital Injection*

Patient No.	Semantic Relatedness	Naming	Reading
	Intact Group (by Left Injection)		
4	4/4	3/4	4/4
5	4/4	4/4	3/4
6	4/4	4/4	4/4
7	4/4	4/4	4/4
8†	4/4	3/4	2/4
Total (n = 5)	**20/20**	**18/20**	**17/20**
	Impaired Group (by Left Injection)		
10	4/4	4/4	4/4
12	4/4	4/4	4/4
13	4/4	4/4	4/4
14	4/4	4/4	4/4
15	4/4	4/4	4/4
Total (n = 5)	**20/20**	**20/20**	**20/20**

*The fraction represents the number correct divided by the total number of items.
†Patient with crossed language dominance.

from patient 4's EEG were unavailable). As a measure of the perfusion of amobarbital in the posterotemporal-inferoparietal region, the degree of slowing seen in the T_3-T_5 electrode pair (left anterior temporal to posterior temporal sites) was compared with that seen in the left F_7-T_3 pair (left inferior frontal to anterior temporal sites), along with similar comparisons of the activity on the right side. In all patients but patient 14, slowing was greater anteriorly than posteriorly; in patient 14, the degree of slowing seen in the two derivations was equal. Therefore, for all subjects except patient 14 the degree of slowing posteriorly was less than the degree of slowing anteriorly, with no correlation with performance on the semantic-relatedness task.

Whether subjects could perform the semantic-relatedness task was not significantly related to age ($t = 1.4$, $P = .18$). However, subjects who failed the task did have a significantly shorter duration of seizures than did those who passed the test (6.4 years vs 18.2 years, respectively) ($t = 2.59$, $P = .03$). Also, those who failed the test were much more likely to have had a visible lesion on either side than did those who did not fail (six vs one, significant by both χ^2 and sign tests, $P \leq .01$). Time of testing following the amobarbital injection did not show a significant difference in the performance of the semantic-relatedness task for the left hemisphere injections (for intact vs impaired performance, $t = -.23$, $df = 13$, $P = .82$). The semantic-relatedness task after right hemisphere injection was performed earlier, on the average, than were the semantic-relatedness tasks after left hemisphere injection ($t = -2.44$, $df = 23$, $P = .02$). Despite this earlier testing, during a time of, presumably, greater effect from the amobarbital injections, no deficit was found on the semantic-relatedness task after the right hemisphere injections, as noted earlier.

COMMENT

Patients who received left hemisphere amobarbital injections were generally severely impaired in their ability to read aloud or name pictures after receiving the injection, except for the patient with crossed dominance. Despite these language impairments, our critical finding was that 53% of these patients were, nevertheless, able to match perfectly the same visually presented words to their corresponding pictures by their meanings or associations. If the four patients who were left-handed or showed crossed or mixed dominance on amobarbital testing are excluded, the percentage is even greater (58%). We suggest that the most parsimonious explanation of this sparing is that, even though the left posterotemporal-inferoparietal region is critical for this ability, this region may not be sufficiently affected by intracarotid amobarbital infusion in those individuals with spared performance.

Previous work has established that correct performance on the semantic-relatedness task is critically dependent on the integrity of the posterotemporal-inferoparietal region, but only in the left (dominant) hemisphere.[8,9] Right hemisphere lesions do not cause semantic errors on picture-word matching,[11] although other semantic functions are influenced by the right hemisphere.[12,13]

Individual variability in vascular supply is well recognized. It appears that the posterotemporal-inferoparietal region is variably nourished by both the middle cerebral artery and the posterior cerebral artery,[14,15] with a watershed area supplied by both.[16] Patients with infarcts in this watershed region typically present with poor comprehension with frequent semantic paraphasias, yet display otherwise fluent speech production.[17] Since the watershed region of infarction typically involves the posterotemporal region, the implication for amobarbital testing is that portions of the posterotemporal region are not principally supplied through the carotid system. Moreover, the portions that are supplied through the carotid system may be subject to dilution and rapid washout, conceivably by the vertebrobasilar system.[18] Therefore, individual variations in vascular supply and, perhaps, in cerebral representation of language,[19-21] seem sufficient to account for the observed individual variations in susceptibility to impairment on semantic relatedness by intracarotid amobarbital injection.

This hypothesized difference in perfusion could not be appreciated with either the arteriographic or EEG techniques used. These techniques, it should be emphasized, may not have been optimal for addressing this question. The arteriographic investigations used pressure injection, while the amobarbital investigations used hand injection. The EEG montage did not cover all regions of possible importance.

Another explanation of these data is possible, although it is one that we think is less likely: the language abilities necessary for the semantic-relatedness task had, somehow, shifted elsewhere in the left hemisphere, or even to the right hemisphere, in those patients who were able to accomplish the task. The cause of this shift would have been the effects of their longer seizure histories or, perhaps, whatever underlying condition led to their seizure disorders, in the absence of a visible-mass lesion. While shifts in intrahemispheric language organization have been demonstrated in patients with chronic epilepsy,[20-22] these shifts almost never occur except with lesions encroaching on the primary speech areas.[22] None of the eight patients who passed our semantic-relatedness test had such lesions. In one patient of this group (patient 1) who had a lesion visible on computed tomographic and magnetic resonance imaging scans, the lesion was in the middle portion of the superotemporal gyrus, outside of the primary speech area as shown by extraoperative direct cortical electrical stimulation[23] and excisional surgery.

It is even less likely that our data are due to a displacement of language functions to the opposite hemisphere. None of the eight patients who passed the semantic-relatedness task after amobarbital injection into the left carotid artery had the lesions that have been associated with such a shift.[22] More direct evidence comes from the finding that five of these eight patients who also received an amobarbital injection into the right carotid artery presented with no impairment of semantic comprehension. Additionally, seven of eight patients had other language functions still strongly lateralized to the left hemisphere. This was shown by intracarotid amobarbital testing in all patients and by the impairment of both speech comprehension and production in response to direct cortical electrical stimulation in three of eight patients who also underwent such mapping.[23] In general, the right hemisphere does not appear to normally possess the ability to independently make judgments of semantic relatedness. Evidence for this finding comes from (1) patients who underwent a left hemispherectomy,[24] and (2) lateralized right hemisphere testing of patients who underwent a commissurotomy.[25,26] Therefore, the possibility that the right hemisphere could be performing this function in our subjects seems remote.

Therefore, the significance of these data is the following: the intracarotid amobarbital test can be used reliably only for determining lateralization of speech-production ability and other functions subserved by the anterior circulation. The intracarotid amobarbital test does not reliably assess all of the speech-comprehension functions subserved by the posterior circulation.

More generally, the intracarotid amobarbital test cannot be expected to reliably affect the functions of the posterior territory of the middle cerebral artery. Therefore, conclusions drawn from the intracarotid amobarbital test about the laterality (or lack thereof) of functions thought to be associated with these regions, such as attentional mechanisms,[27] may have to be interpreted with caution.

The practical significance of our data is that the intracarotid amobarbital test cannot be completely relied on to determine the laterality of all language functions, because of the variable perfusion to some regions the dominant hemisphere subservin language and the occurrence of ind viduals in whom speech comprehe sion is not subserved by the sam hemisphere as speech production. This may be important when the po sibility of surgical encroachment o these regions is present, which is no a more frequent possibility in foc cortical resections for epilepsy o tumor.[29] It may necessitate the nee for other diagnostic studies, such a intraoperative and extraoperative direct cortical electrical stimulation fo language localization[30,23] or selectiv amobarbital injection into the posterior cerebral artery.[31]

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References

1. Wada J. A new method for the determination of the side of cerebral speech dominance: a preliminary report on the intracarotid injection of sodium amytal in man. In Japanese. *Med Biol.* 1949;14:221-222.

2. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance. *J Neurosurg.* 1960;17:266-282.

3. Branch C, Milner B, Rasmussen T. Intracarotid sodium amytal for the lateralization of cerebral speech dominance. *J Neurosurg.* 1964; 21:399-405.

4. Blume WT, Grabow JD, Darley FL, Aronson AE. Intracarotid amobarbital test of language and memory before temporal lobectomy for seizure control. *Neurology.* 1973;23:812-819.

5. Milner B. Psychological aspects of focal epilepsy and its neurosurgical management. *Adv Neurol.* 1975;8:299-321.

6. Lesser RP, Dinner DS, Lueders H, Morris HH. Memory for objects presented soon after intracarotid amobarbital sodium injections in patients with medically intractable complex partial seizures. *Neurology.* 1986;36:895-899.

7. McGlone J. Speech comprehension after unilateral injection of sodium amytal. *Brain Lang.* 1984;22:150-157.

8. Gainotti G, Silveri MC, Villa G, Miceli G. Anomia with and without lexical comprehension disorders. *Brain Lang.* 1986;29:18-33.

9. Hart J, Gordon B. Delineation of single-word semantic comprehension deficits in aphasia, with anatomic correlation. *Ann Neurol.* 1990;27:226-231.

10. Milner B, Branch C, Rasmussen T. Study of short-term memory after intracarotid injection of sodium amytal. *Trans Am Neurol Assoc.* 1962;87:224-226.

11. Gainotti G, Caltagirone C, Miceli G. Semantic disorders of auditory language comprehension in right brain-damaged patients. *J Psycholinguist Res.* 1979;8:13-20.

12. Wapner W, Hamby S, Gardner H. The role of the right hemisphere in the apprehension of complex linguistic materials. *Brain Lang.* 1981;14:15-33.

13. Chiarello C. Hemisphere dynamics in lexical access: automatic and controlled priming. *Brain Lang.* 1985;26:146-172.

14. Damasio H. A computed tomographic guide to the identification of cerebral vascular territories. *Arch Neurol.* 1983;40:138-142.

15. Stephens RB, Stilwell DL. *Arteries and Veins of the Human Brain.* Springfield, Ill: Charles C Thomas Publisher; 1969.

16. Wodarz R. Watershed infarctions and computed tomography: a topographical study in cases with stenosis or occlusion of the carotid artery. *Neuroradiology.* 1980;19:245-248.

17. Bogousslavsky J, Regli F. Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications. *Ann Neurol.* 1986; 20:346-350.

18. Meyer JS, Denny-Brown D. The cerebral collateral circulation, I: factors influencing collateral blood flow. *Neurology.* 1957;7:447-458.

19. Whitaker HA, Selnes OA. Anatomic variations in the cortex: individual differences and the problem of the localization of language functions. *Ann N Y Acad Sci.* 1976;280:844-854.

20. Ojemann GA, Whitaker HA. Language localization and variability. *Brain Lang.* 1978; 6:239-260.

21. Ojemann GA. Individual variability in cortical localization of language. *J Neurosurg.* 1979;50:164-169.

22. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralization of cerebral speech functions. *Ann N Y Acad Sci* 1977;299:355-369.

23. Lesser RP, Lueders H, Klem G, et al. Extraoperative cortical functional localization in patients with epilepsy. *J Clin Neurophysiol* 1987;4:27-53.

24. Day PS, Ulatowska HK. Perceptual, cognitive, and linguistic development after early hemispherectomy: two case studies. *Brain Lang* 1979;7:17-33.

25. Levy J, Trevarthen C. Perceptual, semantic and phonetic aspects of elementary language process in split-brain patients. *Brain.* 1977 100:105-118.

26. Gazzaniga MS. Right hemisphere language following brain bisection. *Am Psychol.* 1983; 38:525-537.

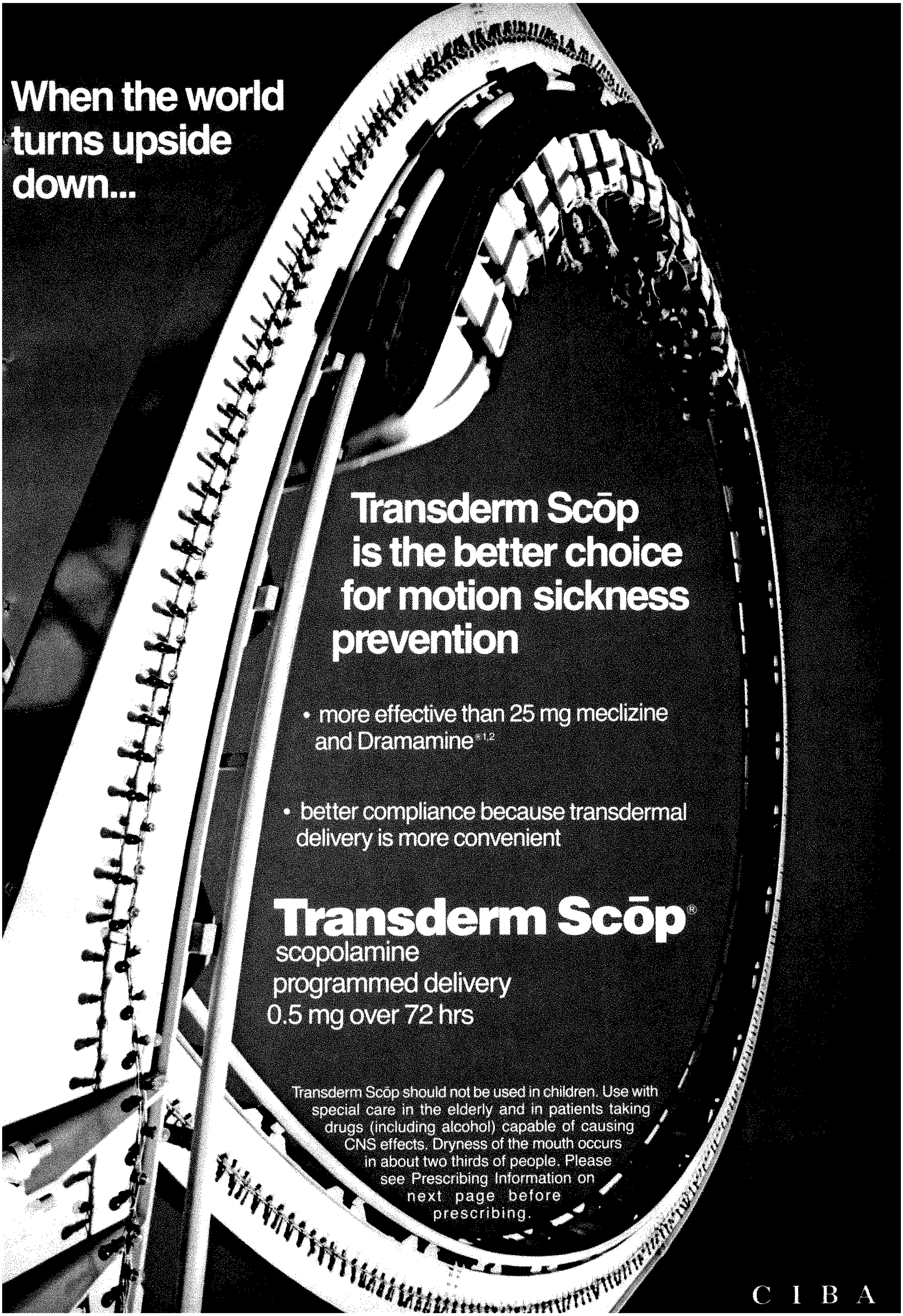
27. Huh K, Meador KJ, Loring DW, Lee GP, Brooks BS. Attentional mechanisms during the intracarotid amobarbital test. *Neurology.* 1989; 39:1183-1186.

28. Selnes OA, Risse GL, Rubens AB, Levy R. Transient aphasia with persistent apraxia: uncommon sequela of massive left hemisphere stroke. *Arch Neurol.* 1982;39:122-126.

29. Morris HH, Lueders H, Hahn JF, Lesser RP, Dinner DS, Estes ML. Neurophysiological techniques as an aid to surgical treatment of primary brain tumors. *Ann Neurol.* 1986;19:559-567.

30. Ojemann GA. Mapping of neuropsychological language parameters at surgery. *Int Anesthesiol Clin.* 1986;24:115-131.

31. Jack CR, Nichols DA, Sharbrough FW, Marsh WR, Petersen RC. Selective posterior cerebral artery amytal test for evaluating memory function before surgery for temporal lobe seizure. *Radiology.* 1988;168:787-793.



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0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

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Transderm Scōp®

scopolamine
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BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

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References:

1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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Memory Complaints in Older Adults

Fact or Fiction?

Karen I. Bolla, PhD; Karen N. Lindgren; Cathy Bonaccorsy; Margit L. Bleecker, MD, PhD

• Complaints of poor memory by patients may be an early symptom of a pathologic process like Alzheimer's disease. It is therefore important to determine if patients' complaints of memory impairments are an accurate reflection of real memory disturbance. The relationship between memory complaints (metamemory) and objective memory performance, mood, age, verbal intelligence, and sex was examined in a group of 199 healthy, community dwelling adults (39 to 89 years old). Memory complaints demonstrated a stronger association with depressed mood than with performance on memory tests. Increasing reports of depressive symptoms were associated with more overall memory complaints. Verbal intelligence, age, and sex also contributed to memory complaints. Patients with higher verbal intelligence reported fewer complaints and placed less emphasis on forgetting. Older individuals reported greater frequency of forgetting and greater frequency of using memory techniques. Specific types of memory complaints, seriousness of forgetting, and types of memory aids employed are also described. These results showed that self-rating of memory disturbance by older adults may be related more to depressed mood than to poor performance on memory tests.

(*Arch Neurol.* 1991;48:61-64)

Increasing attention has been focused on Alzheimer's disease both by the scientific community and the media. As a result, health care providers have become more aware and concerned when their patients complain of memory difficulties. Memory disturbance has been associated not only with disease processes such as Alzheimer's disease and cerebrovascular disease but also with metabolic disturbances, toxic effects of medications, and disturbances of mood (ie, depression).[1] Information relating the accuracy of these complaints to actual memory problems could aid the physician in formulating a more accurate diagnosis for their patients who complain of memory difficulties.

The relationship between metamemory (knowledge of one's own memory abilities), age, objective memory performance, and mood states is unclear. Several studies have found older individuals more accurately evaluated their memory performance than younger individuals,[2-4] while others have found exactly the opposite.[5] There is also evidence for no relationship between age and metamemory abilities.[6-8] These inconsistencies appear to be related to the type of memory task employed as well as the wording of questionnaire items.[8-10]

Do patients' memory complaints predict real memory disturbance as measured on objective memory tests? While Riege[4] found individuals with memory complaints were more likely to score low on memory tests, other authors[7,11] have not found a relationship between memory complaints and impaired memory performance. It may be that older individuals experience the same commonplace incidents of forgetfulness as younger individuals, but interpret these incidents as indications of much more serious problems.[7,11] This tendency has been found to be particularly pronounced in depressed individuals.[3,7] Fifty-one percent of patients referred for formal memory testing because of memory complaints were found to have no objective evidence of memory difficulties, but they were found to have significantly depressed mood.[12] In the healthy elderly, Larrabee and Levin[13] found that ratings of decline in memory function were related to affective states rather than to poor performance on a test of everyday memory. In depressed individuals, changes in level of depression, rather than memory skills training, resulted in more positive self-evaluations of memory.[11,14]

The primary aim of this study was to examine the association between memory complaints and performance on standardized neuropsychologic memory tests, mood, sex, native intelligence, and age in a healthy adult community-dwelling population. The prevalence of specific types of memory complaints, ratings of the seriousness of forgetting in specific situations, and the frequency of techniques used to remember things were also examined.

SUBJECTS AND METHODS

Subjects

The subjects were 199 white volunteers (79 men and 120 women), with age ranging from 39 to 89 years (mean, 62 ± 13 years) and education ranging from 7 to 21 years (mean, 15 ± 3 years). The number of sub-

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From the Department of Neurology (Drs Bolla and Bleecker and Mss Lindgren and Bonaccorsy) and Psychiatry and Behavioral Science (Dr Bolla), The Johns Hopkins University School of Medicine, Baltimore, Md.

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Table 1.—Participants in Each Age Decade*

Decade	Men	Women
39-49	21	19
50-59	12	27
60-69	21	29
70-79	15	31
80-89	10	14
Total	**79**	**120**

*N = 199.

Table 2.—Scores on the GDS, MMQ, and Memory Tests*

	Mean ± SD	Range
Vocabulary†	55 ± 9	20-68
Logical Memory		
Immediate	10 ± 3	2-19
Delayed	8 ± 4	0-18
Verbal-Verbal, trial 4	7 ± 3	0-10
RAVLT, trial 5	12 ± 2	5-15
Visual reproduction	9 ± 3	2-14
GDS	6 ± 4	0-16
Metamemory total	275 ± 46	121-380

*GDS indicates Geriatric Depression Scale; MMQ, Metamemory Questionnaire; and RAVLT, Rey Auditory Verbal Learning Test.

†Wechsler Adult Intelligence Scale-Revised raw score.

Table 3.—Stepwise Regression on Metamemory Scale Category*

	Step	Variable Entered	P	Increase in R^2	Total R^2
M1 General rating of memory	1	GDS	.01	.09	.09
M2 Retrospective evaluation of memory	. . .	. . .	. . .	. . .	. . .
M3 Frequency of forgetting in various situations	1	GDS	.01	.10	.21
	2	WAIS-R vocabulary	.01	.05	
	3	Age	.01	.06	
M4 Reading a novel	1	GDS	.01	.09	.14
	2	LM	.01	.05	
M5 Ability to remember occurrences recent and remote in time	1	GDS	.01	.11	.11
M6 Importance of forgetting when it occurs in various situations	1	GDS	.01	.06	.10
	2	WAIS-R vocabulary	.01	.04	
M7 Reading a newspaper or magazine	1	GDS	.01	.08	.10
	2	DLM	.05	.02	
M8 Frequency of usage of various mnemonics	1	Age	.01	.05	.11
	2	Sex	.01	.04	
	3	GDS	.05	.02	
M9 Effort to avoid forgetting in various situations	1	GDS	.01	.14	.14
Total score	1	GDS	.01	.14	.16
	2	WAIS-R vocabulary	.01	.02	

*GDS indicates Geriatric Depression Scale; WAIS-R, Wechsler Adult Intelligence Scale-Revised; LM, logical memory; and DLM, delayed logical memory.

Table 4.—Frequency of Complaints* and Seriousness† of Memory Problems in Specific Situations

Situation	Complaint, %‡	Seriousness, %‡
Names	83	46
Where you put things (eg, keys)	60	54
Telephone numbers you have just checked	57	45
Words	53	47
Knowing whether you have already told someone something	49	45
Things people tell you	49	49
Faces	42	41
Directions to places	41	45
Beginning to do something and forgetting what you are doing	41	47
Losing the thread of thought in conversation	41	66
Remembering things you have done (ie, lock door, turn off stove)	38	53
Appointments	34	58
Telephone numbers used frequently	29	41

*How often do these present a memory problem to you?

†When you actually forget in these situations, how serious of a problem do you consider memory failure to be?

‡Percent represents only those responding 1, 2, and 3 on the five-point scale (ie, for complaint: 1, always; 3, sometimes; seriousness: 1, very serious; 3, somewhat serious).

jects in each age decade is presented in Table 1. Subjects were included in the study if they never had had head trauma, stroke, seizure, uncontrolled hypertension, pulmonary edema, liver failure, congestive heart failure, uncontrolled thyroid dysfunction, electroconvulsive therapy, sleep disorders, coma, psychiatric disorders, or alcohol/drug abuse. Participants were recruited through newspaper advertisements. This project was approved by the institutional review board and informed consent was obtained following a full explanation of the procedures used in the protocol.

Procedure

A packet of questionnaires was sent to each subject prior to the participant's appointment for a comprehensive neuropsychologic evaluation. Included in the packet were the Geriatric Depression Scale (GDS)[15] and the Metamemory Questionnaire (MMQ).[2] The GDS assesses almost exclusively the psychologic components of depression without somatic complaints. The MMQ[2] is composed of groups of questions related to specific memory categories. The original MMQ was written in a seven-point Likert scale format, but for our purposes, this format was shortened to five points (1, serious problems; 5, no problem). The nine scales measured by the MMQ include: general rating of memory, retrospective evaluation of memory, frequency of forgetting in various situations, ability to remember occurrences recent or remote in time, importance placed on forgetting in various situations, frequency of using various mnemonics, ability to recall what is read in a novel, newspaper, or magazine article, and effort expended to avoid forgetting. Neuropsychologic measures included the Wechsler Adult Intelligence Scale-Revised vocabulary subtest that provides a measure of verbal intelligence[16]; Immediate and Delayed Logical Memory (memory for a short story) and visual reproduction (memory for geometric designs) from the Wechsler Memory Scale[17]; Verbal-Verbal Paired Associates Learning Test (hard associates)[18]; and the Rey Auditory Verbal Learning Test[19] (memory for a 15-item word list presented over five trials).

RESULTS

The average scores on the GDS, MMQ, and memory tests are presented in Table 2. The relationship between metamemory and depression, age, sex, education, verbal intelligence, and memory test performance was evaluated using a stepwise multiple regression. Regressions were performed on the total metamemory scale score as well as the nine individual MMQ scales. A forward stepping entry procedure was used and an F of 4.00 was required for factor entry. The results are given in Table 3. Higher scores on the GDS (greater depression) were as-

Table 5.—Frequency of Techniques Used to Remember Things

	%
Keep an appointment book	69
Make a grocery list	63
Keep things to do in a prominent place where you will notice them	62
Write reminder notes	59
Make lists	59
Keep objects in an identical place so you always know where to find them	58
Plan daily schedule in advance	43
Mental repetition	28
Have others remind you	20

sociated with greater complaints on eight of the nine individual MMQ scales and greater memory complaints overall. Verbal intelligence was related to the total score, the reported frequency of forgetting, and the importance placed on forgetting. Those at higher vocabulary levels reported fewer complaints and placed less importance on forgetting. Age was related to the frequency of forgetting and the frequency of using mnemonic devices. Older subjects reported a higher frequency of forgetting and reported using more mnemonic devices than younger subjects. More women than men reported using memory techniques.

The performance on the logical memory test (paragraph recall) and delayed logical memory test was related to the ease of remembering written material (a novel or a newspaper). When the prevalence of memory complaints was examined, only 19% of the 199 subjects reported no memory complaints. While no age trend was found for the frequency of *total* memory complaints, an aging trend was found for General Rating of Memory (M1). Memory difficulty was reported by 73% of the 40-year-old subjects, 80% of the 50-year-old subjects, 84% of the 60-year-old subjects, 91% of the 70-year-old subjects, and 79% of the 80-year-old subjects.

The specific situations in which memory problems were reported to occur and the rating of their seriousness is given in Table 4. Although forgetting names and forgetting where objects have been placed were reported most frequently, these were not considered serious problems. Instead, losing the thread of thought in conversation and forgetting appointments occurred less often but were believed to be more serious when the situation occurred. There was no change in the frequency of forgetting or concern in specific situations as a function of age. Table 5 lists the frequency in which specific techniques are used to remember things. Written documentation (ie, appointment books, notes, lists) is used most frequently, while relying on others for reminders is the least used memory aid.

COMMENT

Memory complaints in healthy community-dwelling older adults were related more to depressed mood than to performance on objective memory tests. Verbal intelligence, age, and sex were associated with the reporting of memory disturbance. These results agree with those found by other investigators.[3,12,13,20]

Depressed mood is generally associated with diminished ability to think or to concentrate.[21] These attention and concentration difficulties are often misinterpreted as memory disturbance by the patient. Once the distinction between disturbances in concentration vs memory disturbance is discussed with the patient, their fear of having a disease like Alzheimer's is quickly alleviated. It should be kept in mind that none of our subjects would be considered clinically depressed, and therefore these results indicate that even mild complaints of depressed mood appear to influence perceptions of memory.

Questions on the MMQ relating to frequency of forgetting while reading a novel, newspaper, or magazine were positively correlated with performance on the logical memory test (immediate and delayed recall). This relationship could be related to the fact that text recall after only one presentation of the material is more susceptible to disturbances in attention/concentration, a concomitant of depressed mood, than the other memory tasks where the material was given to the participant more than once. A similar interpretation was offered by Larrabee and Levin[22] in their investigation of the association of memory report and performance. A relationship between subjective memory reports and performance on memory tests has previously been found for text or story recall, a common everyday activity.[4,23] Additionally, if material cannot be remembered immediately after it is presented, then poor retention (delayed recall) would also be expected.

The participants with higher verbal intelligence reported fewer total complaints, less forgetting, and placed less emphasis on forgetting. One hypothesis may be that those who have read more are better informed about the aging process as well as diseases such as Alzheimer's and may recognize everyday memory problems as nonserious rather than as a sign of dementia. Education level did not enter any of the regression equations. Bolla-Wilson and Bleecker[24] have suggested that vocabulary level is more appropriate than education level when studying older adults. Older individuals may not have had many formal years of education but may have spent many years self-educating.

Although some researchers have suggested that the elderly have difficulty forming effective strategies to help them recall, others have found that "coaching" the elderly in useful strategies improved memory performance.[8] In our sample, the older adults tended to use more mnemonic strategies to help in their recall. The most frequently used techniques included writing notes, making lists, and keeping objects and things in specific places so they could be easily found. Since the majority of our subjects tended to be well educated with average and above average levels of verbal intelligence, this could account for their tendency to formulate their own memory techniques for more effective recall.

Whereas age was not associated with the total number of complaints on the MMQ, age was associated with a greater frequency of forgetting in various situations. While the most common complaints were in the ability to remember names, where objects were placed, and telephone numbers, these were not considered to be the most serious situations. The most serious situations were reported to be losing the thread of thought in conversation and forgetting appointments (although these occurred less frequently). Since reports of forgetting were not related to actual memory ability, it appears that older adults may be more "fine tuned" to situations in which they forget, whereas younger individuals pay less attention to common memory problems.[7]

The ability to remember occurrences, both recent and remote in time, was correlated with the GDS. Older individuals may compare present memory ability with their own past ability, rather than comparing memory ability with individuals their own age. Retrospective comparison produces feelings of inadequacy: normal changes in memory ability are ignored as well as the fact that when younger, one practices memory skills when in school or on a job. Additionally, only a small percent (19%) of our population

failed to report memory complaints. In summary, these results suggest that self-reported memory complaints in healthy older adults appear to be more closely associated with depressed mood than with actual memory performance on standard clinical memory tests.

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References

1. Cummings JL, Benson DF. *Dementia: a Clinical Approach.* Stoneham, Mass: Butterworths; 1983.
2. Zelinski EM, Gilewski MJ, Thompson LW. Do laboratory tests relate to self-assessment of memory ability in the young and old? In: Poon LW, Toyard JL, Cermak LS, Arenberg D, Thompson LW, eds. *New Directions in Memory and Aging.* Hillsdale, NJ: Lawrence Erlbaum Associates; 1980:519-544.
3. Niederehe G, Yoder C. Metamemory perceptions in depressions of young and older adults. *J Nerv Mental Dis.* 1989;177:4-14.
4. Riege WH. Self-report and tests of memory aging. *Clin Gerontol.* 1982;1:23-36.
5. Bruce PR, Coyne AC, Botwinick J. Adult age differences in metamemory. *J Gerontol.* 1982; 37:354-357.
6. Rabinowitz JC, Ackerman BP, Craik FIM, Hinchley JL. Aging and metamemory: the roles of relatedness and imagery. *J Gerontol.* 1982;37:688-695.
7. Kahn RL, Zarit SH, Hilbert NM, Niederehe G. Memory complaint and impairment in the aged: the effect of depression and altered brain function. *Arch Gen Psychiatry.* 1975;32:1569-1573.
8. Lovelace EA, Marsh GR. Prediction and evaluation of memory performance by young and old adults. *J Gerontol.* 1985;40:192-197.
9. Hermann DJ. Know thy memory: the use of questionnaires to assess and study memory. *Psychol Bull.* 1982;92:434-452.
10. West RL, Berry JM, Dennehy D. Self-efficacy and memory performance: measurement issues. Presented at the meeting of the American Psychological Association; August 1987; New York, NY.
11. Zarit SH, Gallagher D, Kramer N. Memory training in the community aged: effects on depression, memory complaint and memory performance. *Educ Gerontol.* 1981;6:11-27.
12. Bolla-Wilson K, Bleecker ML. Memory complaints: dementia or depression? *Gerontologist.* 1986;26:142A.
13. Larrabee GJ, Levin HS. Verbal, visual and remote memory performance in a normal elderly sample. Presented at the 12th Annual Meeting of the International Neuropsychological Society; February 1984; Houston, Tex.
14. Popkin SJ, Gallagher D, Thompson LW, Moore M. Memory complaint and performance in normal and depressed older adults. *Exp Aging Res.* 1982;8:141-145.
15. Brink TL, Yesavage JA, Lum O, Hiersema P, Adey M, Rose TL. Screening tests for geriatric depression. *Clin Gerontol.* 1982;1:37-43.
16. Wechsler D. *Wechsler Adult Intelligence Scales-Revised Manual.* New York, NY: Psychological Corp; 1981.
17. Wechsler D. A standardized memory scale for clinical use. *J Psychol.* 1945;19:87-95.
18. Butters N, Cermak LS. *Alcohol Korsakoff's Syndrome: An Informational Processing Approach to Amnesia.* Orlando, Fla: Academic Press Inc; 1980.
19. Lezak M. *Neuropsychological Assessment.* New York, NY: Oxford University Press Inc; 1983.
20. Williams JM, Little MM, Scates S, Blockman N. Memory complaints and abilities among depressed older adults. *J Consult Clin Psychol.* 1987;55:595-598.
21. Sternberg DE, Jarvik ME. Memory functions in depression: improvement with antidepressant medication. *Arch Gen Psychiatry.* 1976; 33:219-224.
22. Larrabee GJ, Levin HS. Memory self-ratings and objective test performance in a normal elderly sample. *J Clin Exp Neuropsychol.* 1986; 8:275-284.
23. Dixon R, Hultsch D. Metamemory and memory for text relationships in adulthood. *J Gerontol.* 1983;38:689-694.
24. Bolla-Wilson K, Bleecker ML. The influence of verbal intelligence, gender, age and education on the Rey Auditory Verbal Learning Test. *Dev Neuropsychol.* 1986;2:203-211.

ANTICONVULSANT BULLETIN

New evidence: No difference between the cognitive effects of phenytoin and carbamazepine

Turn page for the results of an important new study.

ANTICONVULSANT BULLETIN

Results from:
Comparative cognitive effects of anticonvulsants

K.J. Meador, D.W. Loring, K. Huh, B.B. Gallagher, D.W. King
Neurology. 1990;40:391-394.

Patients receiving phenytoin and carbamazepine had virtually identical cognitive performances[1]

- Fifteen seizure patients treated with phenytoin, carbamazepine, and phenobarbital for 3 months each were given a cognitive evaluation at the end of each treatment period[1]
- Cognitive tests were designed to assess deficits associated with anticonvulsants—impairments in memory, information processing, attention/concentration, and motor speed[1]
- Mean cognitive scores and individual responses failed to suggest a trend toward differential effects[1]

Mean scores* for cognitive measures

Cognitive Measures	Carbamazepine	Phenytoin	Phenobarbital
Grapho-Motor Coding	48	48	43
Simple Attention†	5.5	5.5	5.7
Simple Attention‡	4.0	4.5	4.5
Selective Reminding Test	53	59	49
Repetitive Motor Speed	46	45	44
Coordination/Motor Speed	72	73	74
Decisional/Motor Speed	698	705	737

—adapted from Meador et al, p 392[1]

*On Decisional/Motor Speed, it was desirable to achieve as *low* a score as possible. On all other tests, it was desirable to achieve as *high* a score as possible. However, there was no significant difference between scores of the three anticonvulsants on any test with the exception of Grapho-Motor Coding—the score for phenobarbital was significantly worse than for the other two anticonvulsants

†Digit Span Forward. ‡Digit Span Backward

Rigorous study design helped prevent patient selection bias—a flaw of most earlier studies

- Randomized, double-blind, triple-crossover study design helped prevent patient selection bias[1]
- Dosages were adjusted to be within the standard therapeutic range (phenytoin, 10 to 20 μg/mL; carbamazepine, 6 to 12 μg/mL; phenobarbital, 15 to 40 μg/mL)[1]

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(extended phenytoin sodium capsules, USP) 100 mg

Reference 1. Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. *Neurology* 1990;40:391-394.

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Please see adjacent page for a brief summary of full prescribing information

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Dilantin® KAPSEALS® (Extended Phenytoin Sodium Capsules, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

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In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G280

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Antibodies to Myelin-Associated Glycoprotein Are Found in Cerebrospinal Fluid in Polyneuropathy Associated With Monoclonal Serum IgM

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• Antibodies to myelin-associated glycoprotein (MAG) have been demonstrated in the serum samples from about half the patients with polyneuropathy associated with serum IgM monoclonal component. We examined cerebrospinal fluid (CSF) and serum samples from 13 patients with this disease by enzyme-linked immunosorbent assay for anti-MAG IgM antibodies. We detected these antibodies in both CSF and serum samples in 10 of the patients; in three of them the antibodies were at higher levels in the CSF. The remaining three patients had anti-MAG IgM antibodies in the CSF only. Intrathecal production of anti-MAG IgM antibodies is thus common in polyneuropathy associated with IgM monoclonal component. In three patients, examined on two occasions from 1 to 7 years, high anti-MAG IgM antibody levels persisted in CSF and serum samples. Among 165 patients with other neurologic diseases, including 60 with multiple sclerosis and 60 control subjects with tension headache, anti-MAG IgM antibodies were detected in the CSF from three patients (two with multiple sclerosis, one with aseptic meningitis), and in the serum sample of one patient with multiple sclerosis. Whether the frequent occurrence of anti-MAG IgM antibodies in CSF and their intrathecal synthesis has pathogenetic relevance for the development of polyneuropathy associated with IgM monoclonal component is unsure.

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Polyneuropathy and monoclonal gammopathy of unknown significance are associated,[1,2] and a causal relationship between serum IgM monoclonal component and polyneuropathy has been suggested.[3-7] In about 50% of patients with IgM monoclonal component in serum, the monoclonal IgM has been shown to bind to myelin structures, mainly myelin-associated glycoprotein (MAG),[5,7-9] glycolipids,[10-12] and a 25- to 30-kd peripheral nerve myelin protein.[13-15] Direct injection of serum samples containing monoclonal component together with complement into nerves of appropriate species induces demyelination,[16,17] while systemic injection has not been shown to produce disease despite long-term observation and treatment.[18] The pathogenetic role of antibodies directed against nervous tissue components is, however, not clear in view of (1) occurrence of such antibodies in normal individuals without disease[15,19]; (2) about 50% of polyneuropathy patients with IgM monoclonal component have no defined antibody activity against myelin components; and (3) the failure of disease induction in systemic passive transfer experiments.[18]

In nerve biopsy specimens[20] and in skin biopsy specimens containing nerve fibers,[21] deposits of IgM have been found. Thus, IgM antibodies of putative pathogenetic importance must in some way have reached the endoneurium in spite of the blood-nerve barrier. One mechanism for this could be by local IgM antibody production. To our knowledge, there are no previous studies on antibodies directed against myelin components in the cerebrospinal fluid (CSF) of patients with polyneuropathy and monoclonal IgM component. We describe that anti-MAG IgM antibodies, when present in serum samples from patients with polyneuropathy, are regularly found in CSF, and may even occur in CSF exclusively.

PATIENTS, MATERIALS, AND METHODS

Patients

Thirteen patients (seven women) had chronic sensory/motor polyneuropathy and IgM monoclonal component in serum samples as defined by agarose electrophoresis and immunofixation. A summary of serum and CSF findings is presented in Table 1. The age of the patients varied between 4 and 83 years (mean, 71 years). Patients and 11 had Waldenström's disease, whereas the others had monoclonal gammopathy of unknown significance. Moderate to severe reduction in nerve conduction velocity was present in all patients except patient 3 in whom neurophysiologic signs of denervation were more prominent.

In addition, 16 patients (five women) with polyneuropathy and serum monoclonal component of IgG isotype in 14 patients and of IgA isotype in two patients were examined. The age of the patients ranged from 41 to 83 years (mean, 70 years).

Control subjects consisted of 165 patients (99 women). Their ages ranged from 20 to 8 years (mean, 67 years). Forty-three of the patients had polyneuropathy without monoclonal component in the serum samples, nine had chronic inflammatory demyelinating polyneuropathy, 14 had acute Guillain-Barré syndrome, 60 had clinically definite multiple sclerosis, 14 had acute aseptic meningitis, 20 had lymphocytic meningoradiculitis (Lyme neuroborreliosis), and five had cerebrovascular disease. The polyneuropathy was due to diabetes in two patients, Refsum's syndrome in one, alcoholism in two, vitamin B_{12} deficiency in two, malignancy in one, sarcoidosis in one, Charcot-Marie-Tooth disease in one, was of unknown cause in thirty-one, and was probably hereditary, but not classified, in two.

Sixty subjects (38 women) who had tension headache and no evidence of organic neurologic diseases constituted our "normal" control subjects. Their ages ranged from 20 to 68 years (mean, 43 years). All 60 subjects had normal findings on routine CSF examinations for cell count, CSF:serum albumin ratio, IgG index, and agarose isoelectric focusing for IgG.

Preparation of MAG

Bovine MAG was prepared by the lithium diiodosalicylatephenol method[22] from brain myelin.[23] One single band migrating at 100 kd appeared after sodium dodecyl sulfate electrophoresis,[24] showing the purity of the preparation.

CSF Studies

The CSF cells were counted by phase contrast microscopy. The IgG and albumin levels were measured by immunoprecipitation nephelometry, and IgA and IgM levels were determined by enzyme-linked immu-

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Reprints not available.

Table 1.—Cerebrospinal Fluid (CSF) and Serum Findings in 13 Patients With Polyneuropathy and IgM M Component in Serum Samples*

					Anti-MAG IgM			
		IgM			ELISA		Western Blot	
Patient/ Age, y/Sex	Light Chain Type of IgM M Component	CSF (0.45 mg/L)	Serum Samples (2.7 g/L)	IgM† Index (0.06)	CSF (0.08)	Serum Samples (0.11)	CSF	Serum Samples
1a/65/M	κ	38.0	18.2	0.05	0.50	0.20	ND	+
1b	κ	11.0	21.7	0.03	0.48	0.63	−	+
2/79/F	κ	5.6	19.6	0.02	0.10	0.45	ND	+
3/78/F	λ	8.2	17.0	0.11	0.44	0.11	ND	−
4/79/F	κ	36.0	13.7	0.10	0.61	0.62	+	+
5a/60/F	κ	0.8	3.5	0.09	0.13	0.23	ND	+
5b	κ	1.9	12.0	0.02	0.80	0.71	+	+
6/69/M	κ	15.0	27.5	0.05	0.10	0.27	ND	−
7/79/F	κ	27.0	4.0	0.59	0.65	1.26	ND	+
8a/64/F	κ	31.0	7.8	0.09	0.72	0.90	ND	+
8b	κ	3.7	8.0	0.07	1.00	1.00	ND	+
9/49/M	κ	4.8	8.7	0.07	0.85	1.07	ND	+
10/83/F	κ	0.8	2.5	0.03	0.13	0.23	ND	−
11/70/M	κ	1.1	32.5	0.001	0.45	0.06	ND	−
12/74/M	λ	22.0	32.5	0.03	1.54	1.47	ND	+
13/79/M	κ	31.0	6.4	0.30	0.20	0.03	ND	−

*Numbers within parentheses indicate upper reference values; a and b correspond to concentration specimens from individual patients; M, monoclonal; MAG, myelin-associated glycoprotein; ELISA, enzyme-linked immunosorbent assay; M, male; F, female; ND, not done; plus sign, positive; and minus sign, negative.

†IgM index equal to (CSF/serum IgM):(CSF/serum albumin).[25]

nosorbent assay (ELISA).[25] The CSF:serum albumin ratio was determined as a variable of the blood-brain barrier state.[26] For documentation of intrathecal immunoglobulin synthesis, CSF IgG index was calculated,[26] as were corresponding IgA and IgM indexes.[25]

ELISA for Detection of Anti-MAG IgM and IgG Antibodies

Ninety-six polystyrene microtiter plates (Dynatech M-129B, Dynatech, Zug, Switzerland) were coated overnight at 4°C with 100-μL aliquots containing 1 μg/mL of purified bovine MAG dissolved in phosphate-buffered saline (PBS), and thereafter washed five times in PBS containing 0.05% Tween 20. Wells were blocked with 200-μL per well of PBS containing 2% bovine serum albumin (Sigma Chemical Co, St Louis, Mo). Samples (100 μL) of serum and CSF adjusted to 1 mg/L of IgM were incubated overnight at 4°C. This IgM concentration yielded optimal discrimination between a positive control serum sample and the negative control consisting of pooled normal serum samples. The CSF samples with IgM concentrations less than 1 mg/L were applied undiluted, except for the addition of 20 μL of PBS per 100 μL of CSF. After washing, alkaline phosphatase-conjugated rabbit anti-human IgM antiserum (μ-chain specific, Dako, Copenhagen, Denmark) diluted 1:2000 was added. After incubation at room temperature for 2 hours, plates were washed and incubated with 100 μL per well of substrate *p*-nitrophenylphosphate (1 mg/mL; Sigma Chemical Co) in 10% diethanolamine and 0.02% magnesium chloride buffer, pH 9.8. Plates were read in an automated ELISA spectrophotometer at 405 nm. The enzyme reaction was allowed to continue until an absorbance value of 1.2 was reached for the positive control. Pooled normal serum samples never gave absorbance values above 0.08. Samples were considered positive when the absorbance value was higher than +3 SD of the mean value obtained from analysis of serum samples and CSF from 60 subjects with tension headache. The range of absorbance values for these serum samples was 0 to 0.10 (mean, 0.023) and the range for corresponding CSF samples was 0 to 0.077 (mean, 0.014), yielding a mean value +3 SD of 0.11 for serum samples and 0.08 for CSF.

For detection of anti-MAG IgG antibodies, 96-well polyvinylchloride microtiter plates (Dynatech) were used; coating concentration of MAG was 3 μg/mL; CSF and serum IgG concentrations were adjusted to 10 μg/mL with PBS containing 1% bovine serum albumin; antiserum consisted of alkaline phosphatase-conjugated rabbit anti-human IgG (γ-chain specific, Dako) diluted 1:1000. Plates were read when an absorbance value of about 0.35 was reached for a "positive" control consisting of a serum sample from a patient with aseptic meningitis. Pooled normal serum samples used as negative controls never gave absorbance values higher than 0.03. Samples were considered positive when the absorbance value was higher than +3 SD of the mean value obtained from analysis of serum samples and CSF from 43 subjects with tension headache. Range of absorbance values for these serum samples was from 0 to 0.051 and for CSF from 0 to 0.058, yielding a mean value +3 SD of 0.06 for serum samples and 0.07 for CSF.

Preliminary studies showed no difference when comparing bovine MAG and human MAG as antigen in ELISA.

Western Blot

To confirm the presence of anti-MAG antibodies, we examined serum samples and CSF specimens by Western blot. The CSF specimens of patients 1b, 4, and 5b (Table 1) were concentrated by air pressure using microcollodion bags (Sartorius, Göttingen, Federal Republic of Germany) to achieve an IgM concentration of 600 to 1000 mg/L. Because of the small volumes available, additional CSF specimens could not be examined. Myelin-associated glycoprotein was subjected to sodium dodecyl sulfate electrophoresis in 12.5% polyacrylamide slab gel,[24] followed by transfer to nitrocellulose membranes (0.45-μm pore size; Schleicher & Schull, Kassel, Federal Republic of Germany).[27] The strips containing MAG were then incubated with a 1:100 diluted patient's serum sample or a 1:5 dilution of the patient's concentrated CSF overnight at room temperature on a shaker platform. After several washes in PBS, strips were incubated with rabbit anti-human IgM (μ-chain specific), rabbit anti-human IgG (γ-chain specific) or rabbit anti-human IgA (α-chain specific) antiserum (Dako) diluted 1:500 in the same buffer, followed by immunoenzyme staining.[28] The same positive and negative controls were used in Western blot as for anti-MAG IgM ELISA.

Demonstration of Anti-MAG IgM Antibodies in Relation to Monoclonal IgM in CSF and Serum by Agarose Isoelectric Focusing and Protein Transfer to Nitrocellulose Membrane

To detect total IgM, serum and CSF samples were analyzed after mild reduction with β-mercaptoethanol. Briefly, 5 μg of IgM were mixed with 10 μL of 0.8 mol/L of β-mercaptoethanol (Sigma) and 80 μL of PBS. This mixture was incubated for 13 to 15 minutes. Fifteen microliters of this preparation were subjected to agarose isoelectric focusing.[28] Separation of proteins was performed for 70 minutes at 15 W. Voltage was increased every 20 minutes

Table 2.—Number of Patients Positive vs Examined for Anti-MAG IgM and IgG Antibodies in Cerebrospinal Fluid (CSF) and Serum Samples as Determined by ELISA, and in Serum Samples Only Evaluated by Western Blot*

	ELISA				Western Blot	
	IgM		IgG		Serum Samples	
Diagnosis	CSF	Serum Samples	CSF	Serum Samples	IgM	IgG
Polyneuropathy and with M component						
IgM	13/13	10/13	0/13	0/13	8/13	0/13
IgG	1/14	0/14	0/14	1/14	0/4	0/14
IgA	1/2	0/2	0/2	0/2	ND	0/2
Polyneuropathy without serum M component	0/43	0/43	0/43	5/43	0/6	ND
CIDP	0/9	0/9	0/9	2/9	0/3	ND
Guillain-Barré syndrome	0/14	0/14	ND	ND	ND	ND
Multiple sclerosis	2/60	1/60	1/43	3/43	ND	ND
Aseptic meningitis	1/14	0/14	ND	ND	ND	ND
Neuroborreliosis	0/20	0/20	ND	ND	ND	ND
Cerebrovascular disease	0/5	0/5	ND	ND	ND	ND
Tension headache	0/60	0/60	0/43	0/43	ND	ND

*MAG indicates myelin-associated glycoprotein; ELISA, enzyme-linked immunosorbent assay; M, monoclonal; ND, not done; and CIDP, chronic inflammatory demyelinating polyneuropathy.

starting from 200 V (50 mA) and finishing at 800 V (18 mA). Separated proteins were transferred to nitrocellulose membrane, followed by incubation in PBS containing 1:500 diluted peroxidase-conjugated $(Fab')_2$ fragment of goat anti-human IgM (μ-chain specific, Sigma), and then stained.[28]

To detect anti-MAG IgM antibodies, nitrocellulose membranes were coated overnight at room temperature in 10 μg/mL of MAG in PBS, followed by blocking with 3% bovine serum albumin in PBS for 1 hour. After agarose isoelectric focusing, separated proteins were transferred to MAG-coated nitrocellulose membrane[29] and antibodies bound were detected by immunoenzyme labeling as for total IgM.

Patterns of anti-MAG IgM antibody were compared with those of total IgM obtained in parallel on the same specimens.

RESULTS

A survey of CSF and serum findings for the 13 patients with polyneuropathy and serum IgM monoclonal component is presented in Table 1. All 13 patients had normal CSF cell counts that varied between 1 and 2×10^6/L. Nine patients had elevated CSF:serum albumin ratio as a sign of damage to blood-brain barrier or blood-nerve barrier in the area of nerve roots. Seven patients had increased IgM index, reflecting intrathecal production of IgM. The IgG index was normal in all patients, while the elevated IgA index was registered in five.

Anti-MAG Antibodies Detected by ELISA

Three of the 13 patients with polyneuropathy and IgM monoclonal component had anti-MAG IgM antibodies in CSF only (patients 3, 11, and 13, Table 1). In the remaining 10 patients, anti-MAG IgM antibodies were present in CSF and serum samples, but three of them (patients 1a, 5b, and 12) had higher absorbance values in CSF than in the serum samples. Evidence was thus obtained for intrathecal production of anti-MAG IgM antibodies in six of the 13 patients with polyneuropathy and IgM monoclonal component.

In patients 1, 5, and 8, two consecutive CSF and serum samples covering 1 to 7 years were examined. Anti-MAG IgM antibodies were detected in all consecutive specimens in both compartments.

One of the 14 patients with polyneuropathy and IgG monoclonal component and one of the two patients with polyneuropathy and IgA monoclonal component also had anti-MAG antibodies of IgM isotype (Table 2, Fig 1). These antibodies were present in CSF only, reflecting intrathecal synthesis.

Among the patients of the different control groups, anti-MAG IgM antibodies were found in CSF from two (3%) of the 60 patients with multiple sclerosis and from one (7%) of the 14 patients with aseptic meningitis, and in the serum sample from one patient (2%) with multiple sclerosis (Table 2, Fig 1).

Slightly elevated absorbance values for anti-MAG antibodies of the IgG isotype were observed in the serum sample from one patient with polyneuropathy and IgG monoclonal component, five patients with polyneuropathy without serum monoclonal component, two with chronic inflammatory demyelinating polyneuropathy, and three with multiple sclerosis (Table 2). In CSF, only one patient with multiple sclerosis had anti-MAG IgG antibodies.

The two patients with polyneuropathy and IgA monoclonal component were examined for anti-MAG antibodies of the IgA isotype in CSF and serum samples, with negative results.

Anti-MAG Antibody Reactivity Detected by Western Blot

Western blot confirmed the presence of anti-MAG IgM antibodies in serum samples from eight of 10 patients with polyneuropathy and IgM monoclonal component who were positive by ELISA (Table 1). The remaining three patients were negative by ELISA and also when examined by Western blot. No anti-MAG reactivity was found by Western blot in nine additional serum samples from two of the control groups (Table 2).

Due to the low IgM levels in CSF compared with serum samples, it was not possible to study CSF specimens by Western blot, except in three patients with polyneuropathy and serum IgM monoclonal component (patients 1b, 4, and 5b). Anti-MAG IgM antibody reactivity was detected in two of these three CSF specimens as exemplified for patient 4 in Fig 2. Anti-MAG antibody reactivity appeared as a faint band on the blots incubated with CSF samples when compared with the strong band seen on the blots of serum samples from the same patient, probably due to differences in the IgM concentration between serum and CSF samples.

Relationship Between IgM Monoclonal Components and Anti-MAG IgM Antibody Activity

Serum and concentrated CSF specimens from patients 1b, 4, and 5b (Table 1) and serum specimens from patients 7 and 8b (Table 1) were analyzed for anti-MAG antibody reactivity after separation by agarose isoelectric focusing. Such antibody reactivity was detected in all specimens examined and localized to the IgM monoclonal components as visualized in Fig 2 for CSF and serum samples from patient 4.

COMMENT

In samples from 29 patients with polyneuropathy and serum monoclonal component, anti-MAG IgM antibodies were detected by ELISA in all 13 patients who had monoclonal component of IgM isotype. In three of these patients, anti-MAG IgM antibodies were present in CSF only, while the remaining 10 patients had antibodies in CSF and serum samples (Table 1). Among the 16 patients with polyneuropathy and monoclonal component of IgG or IgA isotype, anti-MAG IgM antibodies were present only in two patients and in CSF exclusively (Table 2). None of our control subjects with polyneuropathy without serum monoclonal component had anti-MAG IgM antibodies detected by ELISA.

We used a standardized IgM concentration in the ELISA for anti-MAG and may therefore anticipate intrathecal anti-MAG IgM antibody synthesis in patients where CSF absorbance values exceed serum values (Table 1). This was the case in six of the 13 patients with IgM monoclonal component. We therefore propose that patients with polyneuropathy and IgM monoclonal component also be examined for anti-MAG IgM antibodies in CSF. Further studies on larger patient groups are, however, warranted to evaluate the diagnostic and therapeutic implications of such examinations.

When injected directly into peripheral nerves of suitable species, anti-MAG antibodies of the IgM isotype produced demyelination.[16,17] These observations reinforce the possibility that intrathecal production of these antibodies, as we have demonstrated, may indeed have importance for the development of the polyneuropathy. These antibodies might reach the target in the peripheral nerve system, at least at nerve root level, without the need for passage from serum through the blood-nerve barrier.

Since MAG is a normal constituent of the central nervous system, there is also the possibility for central nervous system damage as a result of the intrathecal anti-MAG antibody production. This has been supported by experimental studies, such as injection of mammalian optic nerves with a monoclonal anti-MAG antibody together with complement, which indeed produced demyelination.[30] It is, however, not clear if patients with anti-MAG antibodies have some subclinical central nervous system damage in addition to their overt polyneuropathy.

We could demonstrate that the anti-MAG reactivity was within the IgM monoclonal component in the five serum samples and the three CSF specimens that were analyzed. In these patients, the anti-MAG antibodies were

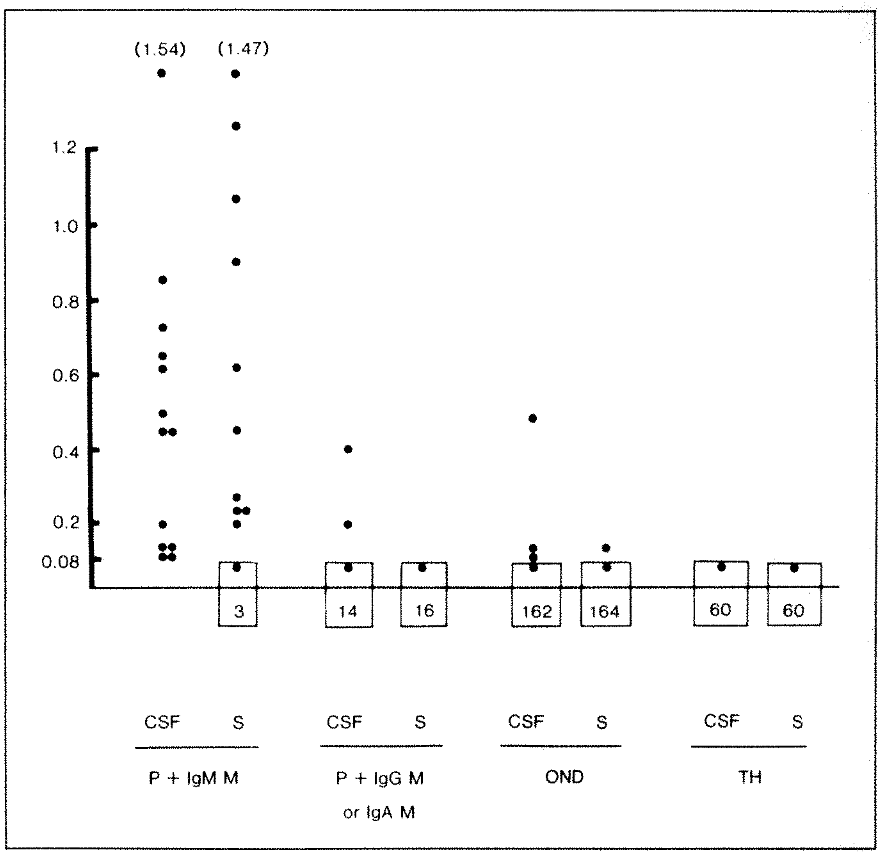

Fig 1.—Anti-myelin-associated glycoprotein (MAG) IgM antibodies determined by enzyme-linked immunosorbent assay in cerebrospinal fluid (CSF) and serum samples (S) from 13 patients with polyneuropathy (P) and IgM monoclonal (M) component, 16 with polyneuropathy and IgG or IgA M component, 165 with other neurologic diseases (OND) and 60 with tension headache (TH). Cut-off limit for CSF is OD = 0.08, and for serum optical/density = 0.11. Numbers in squares correspond to numbers of subjects in each group who had values below these cut-off limits.

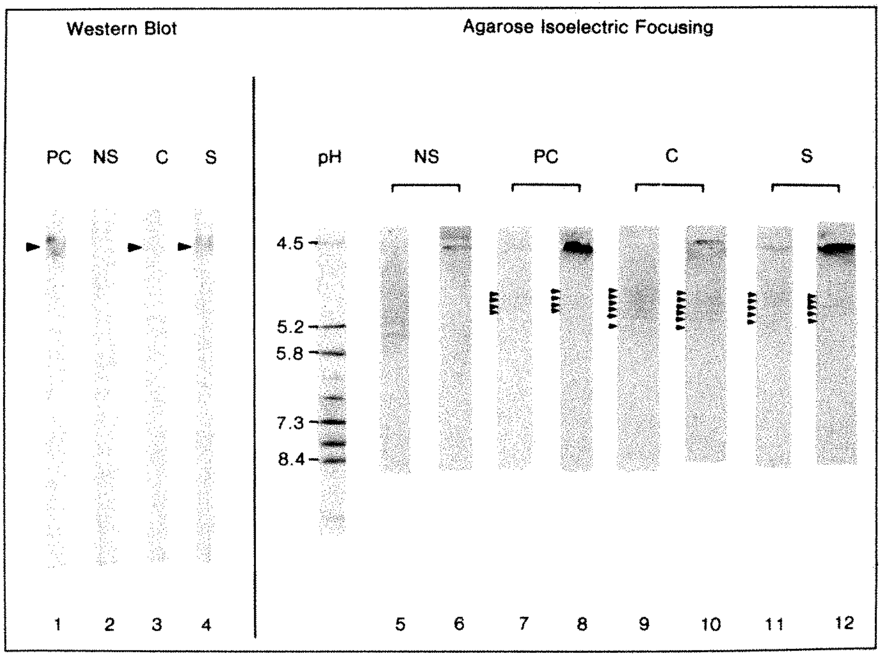

Fig 2.—Demonstration in patient 4 of anti-myelin-associated glycoprotein (MAG) IgM antibody reactivity (arrowheads) in cerebrospinal fluid (CSF) (3) and serum (S) samples (4), using Western blot (to the left). Migration patterns of IgM (arrowheads) on agarose isoelectric focusing in CSF (9) and serum samples (11), and of anti-MAG IgM antibodies detected by immunoblot in CSF (10) and serum samples (12). PC indicates positive control; NS, pooled normal serum samples used as negative control; and pH, reference pH markers.

produced by the neoplastic clone of plasma cells. In those five polyneuropathy patients with monoclonal component, who had anti-MAG IgM antibodies exclusively in CSF as demonstrated by ELISA, not enough CSF was available to analyze the migration properties of the anti-MAG antibodies. It is less likely that the anti-MAG antibodies in these patients belong to the systemic neoplastic plasma cell clones. Furthermore, it seems highly unlikely that a second neoplastic plasma cell clone producing anti-MAG occurs intrathecally. The CSF cell counts and clinical course in these patients did not indicate any central nervous system plasma cell dyscrasia or lymphoma. Mechanisms for induction of anti-MAG antibodies in these patients thus remain unclear. One possibility is that they represent an immune response secondary to nerve damage induced by other means, for example, a T-cell-mediated attack. This explanation could also apply to the anti-MAG IgG antibodies found in serum samples from a few of our patients with polyneuropathy without association with serum monoclonal component, and a few of those with chronic inflammatory demyelinating polyneuropathy (Table 2).

Involvement of MAG in the pathogenesis of multiple sclerosis has been suggested due to the observation of preferential loss of MAG in the periphery of multiple sclerosis plaques.[31-33] Attempts to detect anti-MAG antibodies in CSF and serum samples of patients with multiple sclerosis have given conflicting results,[34-37] probably due to different detection methods used (Möller et al[38]). Our low rate of detection of anti-MAG IgM and IgG antibodies in multiple sclerosis by ELISA is in agreement with previous reports using radioimmunoassay.[35,36,38] It is, however, possible that autoreactive antibodies are bound in vivo to target structures and therefore are difficult to detect in CSF by conventional techniques such as ELISA and radioimmunoassay.

We have demonstrated the regular occurrence of anti-MAG IgM antibodies in CSF from a group of patients with polyneuropathy associated with monoclonal component of IgM isotype. In about half of these patients, there was evidence for intrathecal synthesis of these antibodies.

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References

1. Iwashita H, Argiraskis A, Lowitsch K, Spar W. Polyneuropathy in macroglobulinaemia. *J Neurol Sci.* 1974;21:341-354.

2. Kahn S, Riches PG, Kahn J. Paraproteinaemia in neurological disorders, incidence, association and classification of monoclonal immunoglobulins. *J Clin Pathol.* 1980;33:617-621.

3. Forssman O, Bjorkman G, Hollender A, Englund NE. IgM producing lymphocytes in peripheral nerve in a patient with benign monoclonal gammopathy. *Scand J Haematol.* 1973;11:332-335.

4. Latov N, Sherman WH, Nemmi R, et al. Plasma cell dyscrasia and peripheral neuropathy with monoclonal antibody to peripheral nerve myelin. *N Engl J Med.* 1980;303:618-621.

5. Latov N, Broun PE, Groos B, Sherman WH, Penn AS, Chess L. Plasma cell dyscrasia and peripheral neuropathy: identification of the myelin antigens that react with human paraproteins. *Proc Natl Acad Sci U S A.* 1981;78:7139-7149.

6. Nobile-Orazio E, Vietorisz T, Messito MD, Sherman W, Latov N. Anti-MAG IgM antibodies in patients with neuropathy and IgM M proteins: detection by ELISA. *Neurology.* 1983;33:939-942.

7. Kelly J. Peripheral neuropathies associated with monoclonal proteins: a clinical review. *Muscle Nerve.* 1985;8:138-150.

8. Braun PE, Frail DE, Latov N. Myelin associated glycoprotein is the antigen for a monoclonal IgM in polyneuropathy. *J Neurochem.* 1982;39:1262-1265.

9. Steck AJ, Murray M, Meir G, Page N, Perrusseau G. Demyelinated neuropathy and IgM antibody to myelin associated glycoprotein. *Neurology.* 1983;33:19-23.

10. Chou KH, Ilias AA, Evans JF, Quarles RH, Jungwala FB. Structure of a glycolipid reaction with monoclonal IgM in neuropathy and with HNK 1. *Biochem Biophys Res Commun.* 1985;128:383-388.

11. Ilyas AA, Quarles RH, Macintosch TD, et al. IgM in human neuropathy related to paraproteinaemia binds to a carbohydrate determinant in the myelin associated glycoprotein and to a ganglioside. *Proc Natl Acad Sci U S A.* 1984;81:1225-1229.

12. Miyatani NM, Hiroko B, Sato S, Nakamura K, Tatuhiko Y, Tadashi M. Antibody to syalosyllactosamynilparagloboside in a patient with paraproteinaemia and polyradiculoneuropathy. *J Neuroimmunol.* 1987;14:189-196.

13. Nobile-Orazio E, Hays AP, Latov N, et al. Specificity of mouse and human monoclonal antibodies to myelin-associated glycoprotein. *Neurology.* 1984;34:1336-1342.

14. O'Shanessy DJ, Ilyas AA, Dalakas MC, Medel JR, Quarles RH. Specificity of human monoclonal antibodies from patients with peripheralneuropathy. *J Neuroimmunol.* 1986;11:131-136.

15. Cruz M, Ernerudh J, Olsson T, Höjeberg B, Link H. Occurrence and isotype of antibodies against peripheral nerve myelin in serum from patients with peripheral neuropathy and healthy controls. *J Neurol Neurosurg Psychiatry.* 1988;51:820-825.

16. Willison H, Trapp B, Bocher J, Dalakas M, Griffin J, Quarles R. Demyelination induced by intraneural injection of human anti-myelin associated glycoprotein antibodies. *Muscle Nerve.* 1988;11:1169-1176.

17. Hays A, Latov N, Takatsu M, Sherman W. Experimental demyelination of nerve induced by serum of patients with neuropathy and anti-MAG IgM M protein. *Neurology.* 1987;37:242-256.

18. Steck A, Murray N, Justafre JC, et al. Passive transfer studies in demyelinated neuropathy with IgM monoclonal antibodies to myelin associated glycoprotein. *J Neurol Neurosurg Psychiatry.* 1985;48:927-929.

19. McGimnis S, Kohryama T, Yu R, Pesce M, Latov N. Antibodies to sulphated glucouronic acid containing glycosphingolipids in neuropathy associated with anti-MAG antibodies and n
subjects. *J Neuroimmunol.* 1988;17:119-126

20. Smith S, Kahn SN, Lacey BW, et al. Cl
demyelinated neuropathy associated with b
IgM paraproteinaemia. *Brain.* 1983;106:169

21. Jönsson V, Jensen TS, Friss ML, Sch
H, Stisby B, Struck J. Immunoglobulin depo
peripheral nerve endings detected by skin b
in patients with IgM M proteins and neuro
Neurology. 1984;37:303-306.

22. Quarles R, Barbarash G, Filewicz D,
tyre L. Purification and particle characteri
of the myelin associated glycoprotein from
rat brain. *Biochim Biophys Acta.* 1983;75
143.

23. Norton WT, Poduslo SE. Myelination
nerve: method of myelin isolation. *J Neuro*
1973;21:749-757.

24. Laemmli UK. Cleavage of structura
teins during assembly of the bacteriopha
Nature. 1970;227:668-685.

25. Lolli F, Halawa I, Link H. Intratheca
thesis of IgG, IgA, IgM and IgD in untr
multiple sclerosis and controls. *Acta N*
Scand. 1989;80:238-247.

26. Tibbling G, Link H, Öhman S. Princip
albumin and IgG analysis in neurological
ders, I: establishment of reference values.
J Clin Lab Invest. 1977;37:385-390.

27. Towbin H, Staehlin T, Gordon J. Ele
phoretic transfer of proteins from polyac
mide gels to nitrocellulose sheets: procedur
some applications. *Proc Natl Acad Sci U*
1979;76:4350-4354.

28. Olsson T, Kostulas V, Link H. Improve
tection of oligoclonal IgG in CSF by isoel
focusing in agarose double antibody perox
staining and avidin-biotin amplification.
Chem. 1984;30:1246-1249.

29. Cruz M, Olsson T, Ernerudh J, Höjeb
Link H. Immunoblot detection of oligoclon
ti-myelin basic protein IgG antibodies in
brospinal fluid in multiple sclerosis. *Neur*
1987;37:1515-1519.

30. Sergott RC, Brown MJ, Lisak RP, Mill
Antibody to myelin associated glycoprotein
duces central nervous system demyelin
Neurology. 1988;33:422-426.

31. Itoyama Y, Sternberg NH, Webster
Quarles RH, Cohen SR, Richardson EP Jr. Ir
nocytochemical observations on the distribu
of myelin associated glycoprotein and myeli
sic protein in MS lesions. *Ann Neurol.* 1980;
177.

32. Prineas JW, Kwon TT, Sternberger
Lennon VA. The distribution of myelin assoc
glycoprotein and myelin basic protein in ac
demyelinating MS lesions. *J Neuroimm*
1984;6:251-264.

33. Gendelman HE, Pezeshkpour GH, P
man NJ, et al. A quantitation of myelin assoc
glycoprotein and myelin basic protein loss i
ferent demyelinating diseases. *Ann Neurol.*
18:334-338.

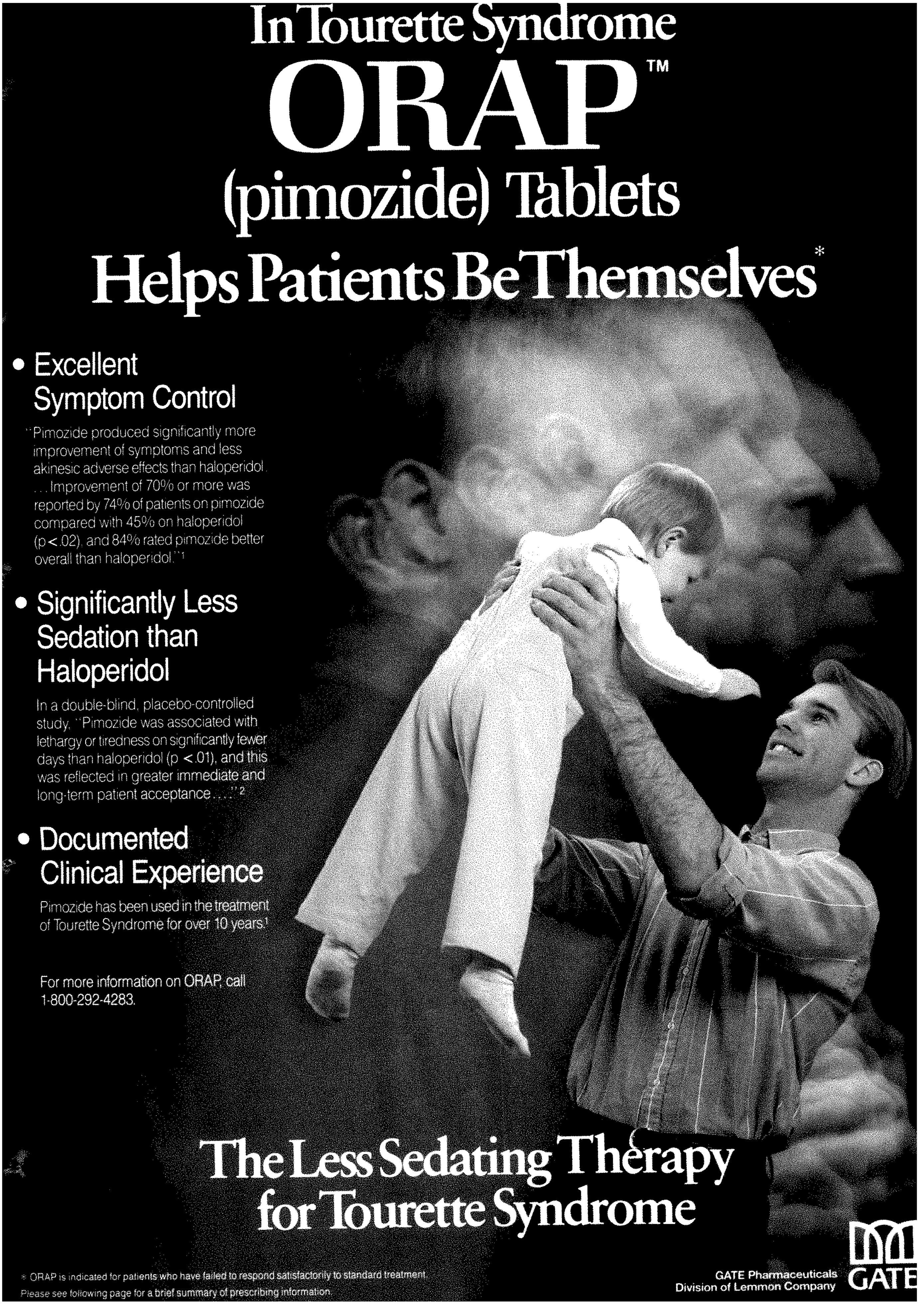
34. Wajgt A, Górny M. CSF antibodies t
elin basic protein and myelin associated g
protein in MS: evidence of the intrathecal
duction of antibodies. *Acta Neurol S*
1983;68:337-343.

35. Nobile-Orazio E, McIntosh C, Latov N
ti-MAG antibody and antibody complex: d
tion by radioimmunoassay. *Neurology.* 19
988-992.

36. Nobile-Orazio E, Spagnol G, Scarlat
Failure to detect anti-MAG antibodies by R
CSF of patients with multiple sclerosis. *J*
roimmunol. 1986;11:165-169.

37. Sato S, Baba H, Inuzuka T, Miyata
Anti-MAG antibody in sera from patients
demyelinating diseases. *Acta Neurol S*
1986;74:115-120.

38. Möller J, Johnson D, Brady R, Tourte
WW, Quarles RH. Antibodies to myelin as
ated glycoprotein in the cerebrospinal fluid o
patients. *J Neuroimmunol.* 1989;22:55-61.



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- **Significantly Less Sedation than Haloperidol**

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ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated withTourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under 'Tardive Dyskinesia' except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes. Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day.

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole. Asthenia, chest pain, periorbital edema

Cardiovascular/Respiratory. Postural hypotension, hypotension, hypertension, tachycardia, palpitations

Gastrointestinal. Increased salivation, nausea, vomiting, anorexia, GI distress

Endocrine: Loss of libido

Metabolic/Nutritional: Weight gain, weight loss

Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia

Psychiatric. Excitement

Skin: Rash, sweating, skin irritation

Special Senses: Blurred vision, cataracts

Urogenital. Noctura, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

Made in Canada

Manufactured by:
McNeil Pharmaceutical, (Canada) Ltd.
Stouffville, Ontario L4A 7x7

Printed in USA
Rev. A 6/88

GATE
GATE Pharmaceuticals
Division of Lemmon Company

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

On Drawing Impairment in Alzheimer's Disease

Andrew Kirk, MD, Andrew Kertesz, MD

• Spontaneous drawings of 38 patients, diagnosed by the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria as "probable Alzheimer's disease," and of 39 normal control subjects were analyzed by two independent observers using a standardized scoring system. Drawings of patients with Alzheimer's disease displayed fewer angles, impaired perspective and spatial relations, simplification, and overall impairment compared with those of the control subjects. This represents a combination of the deficits seen following right- *and* left-hemisphere lesions. Neglect, tremor, and perseveration were not prominent. Drawing impairment was relatively independent of language or memory impairment, but drawing performance was related to perceptual *and* executive dysfunction in the visuospatial domain. Deterioration was followed up for up to 3 years.

(*Arch Neurol.* 1991;48:73-77)

Deficits in constructional abilities, including drawing, are often early signs of degenerative dementia.[1-3] The importance of investigating these aspects of dementia has been brought out by Henderson et al,[4] who demonstrated that patients with Alzheimer's disease (AD) who perform poorly on drawing tasks more often wander and become lost, making their management difficult and predisposing them to complications.[5] Despite the obvious clinical relevance of constructional ability and despite a sizable body of literature contrasting the characteristics of drawing impairment after right- and left-hemisphere damage,[6-22] comparatively little is known about how dementia affects constructional performance.

Following Kleist's[23] 1922 work on "constructional apraxia," there were some early descriptions of constructional disability in dementia, notably by Lhermitte and Trelles[24] and by Mayer-Gross.[25] In retrospect, most of the latter's cases probably represented multi-infarct dementia. Gainotti[26] confirmed and refined Mayer-Gross's[25] observations on *closing-in*—a tendency (uncommon in those with unilateral cerebral damage) for demented patients to draw directly on the model in copying tasks.

Benton and Fogel[27] documented a high incidence of constructional disability in patients with unspecified "diffuse or bilateral lesions," compared with control subjects and with subjects with single lesions. Villa et al[28] contended that coexistent mental deterioration is an important determinant of the degree of constructional disability in patients with unilateral lesions. The relevance of these results to AD is uncertain, especially in light of the demonstration, in a small number of patients with AD, that drawing may be more impaired in those with positron emission tomographic evidence of more marked right than left parietal hypometabolism.[29] It is thus unclear whether drawing disability in AD is a result of widespread cerebral dysfunction or is instead due to damage to specific cortical areas.

Since Paterson and Zangwill's[30] pioneering 1944 investigation, several authors[7,9,13,22,31-33] have confirmed that, despite tremendous variability, the drawings of patients with right-brain damage (RBD) tend to display hemispatial neglect and a piecemeal approach in which individual details may be represented well but are not placed in accurate spatial relationship with one another. On the other hand, patients with left-brain damage (LBD) produce simplified, tremulous drawings with fewer angles.[7-9,13,22,32,33] On the basis of such qualitative differences, Duensing,[34] Piercy et al,[6] and McFie and Zangwill[35] developed the hypothesis that RBD drawing disability is due to a visuoperceptual deficit, while LBD drawings are impaired by an executive defect. This formulation has not been borne out by later investigators,[7,36,37] who found that patients with constructional disability performed more poorly on visuoperceptual tests than did those without constructional disability, no matter which hemisphere was damaged. Detailed investigations along these lines have not, to our knowledge, been carried out in AD. It is not clear whether patients with AD make typical RBD errors, LBD errors, both, or neither. The roles of perceptual vs executive deficits in AD construction also remain to be elucidated.

Drawing is known to worsen as AD progresses,[1,38] but the relationship between deterioration of construction and of other cognitive functions, such as language and memory, has important implications with respect to how cognition is impaired in AD. *Stage* models of AD propose simultaneous and homogeneous deterioration of disparate functions as the disease progresses[39,40]; on the other hand, *subgroup* models postulate separate populations of patients characterized by predominance of one or another type of symptom, especially early in the illness.[41] As drawing impairment parallels impairment of comprehension in patients with LBD,[14,16,22] the interaction between drawing and aphasia is particularly important.

Using a standardized rating system, previously demonstrated to be an effective instrument in the study of drawing after focal cerebral damage,[22]

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we compared the spontaneous drawings of patients with probable AD with those of control subjects to determine how drawing is affected by AD. Retesting examined drawing deterioration with disease progression. Through concomitant testing of other neuropsychologic functions, we explored the relationships between drawing, memory, language, and visuoperceptual function in AD. Using computed tomography and magnetic resonance imaging, we hoped to ensure a more homogeneous group of patients than were included in studies of drawing in dementia from the pre-computed tomography era.[25,26]

Table 1.—Criteria Used to Rate Drawings*

Items Rated on 0-3 Scale

Scale
  0, normal
  1, mildly abnormal
  2, moderately abnormal
  3, severely abnormal
Overlap
  Tendency for separate drawings to be superimposed (single rating for all drawings)
Spatial relationships
  Tendency for components of drawings to be put together abnormally with respect to one another in a piecemeal fashion, so that the whole picture is distorted, resembling an "exploded diagram"
Simplification
  Tendency to oversimplify the drawing, leaving out details
Angle production
  Difficulty forming angles with a tendency to represent them as gaps, scrawls, or curved lines (circle not rated)
Perseveration
  Tendency to redraw lines, parts of the drawing, or the entire drawing
Tremor
  Tendency for lines to be shaky
Perspective
  Tendency for three-dimensional perspective to be poorly represented (only cube, house, and person rated)
Overall impairment
  Rating of each drawing as a whole.

Items Rated on −3 to +3 Scale

Scoring system as above but with negative numbers indicating leftward error and positive rightward
Orientation
  Tendency for drawings to be placed diagonally on the page. Sign indicates the side away from which the drawing leans (circle not rated)
Neglect
  Tendency for one side of the drawing to be incomplete or underdeveloped
Displacement
  Tendency for drawings to be displaced toward one side of the page (single rating for all drawings)

Items Counted

Details
  Total No. of details included (eg, numbers, hands, windows, facial features)
Details externalized
  No. of details incorrectly placed outside rather than inside the outline of the drawing (circle and square not rated)
Angles
  Total No. of angles drawn and percentage acute, right, and obtuse (clock, tree, and person not rated)
Redrawn lines
  No. of lines that have been overdrawn at least once
Line production
  Total No. of lines drawn (only circle, square, and cube rated)
Line joining
  No. of gaps separating lines that should meet
Line crossing
  No. of crossings of lines that should just meet
Extras
  No. of items spontaneously drawn in addition to those requested (single rating for all drawings)

*From Kirk and Kertesz.[22]

PATIENTS AND METHODS

Patients

Thirty-eight patients diagnosed as "probable AD,"[42] according to the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria and 39 normal control subjects were included in our study. Because of the documented importance of impaired comprehension in drawing disability,[14,16,22] we were careful not to exclude subjects with AD on the basis of aphasia. Exclusions were made only if there was diagnostic uncertainty after complete neurologic and laboratory assessment, or if there was a history of stepwise progression, stroke, or other neurologic disease. Control subjects were patients' spouses, hospital employees, and other volunteers without history of neurologic disease or of any other illness likely to impair drawing (eg, substantial arthritis). Control subjects were required to score above 124 on the Mattis Dementia Rating Scale.[43] The two groups did not significantly differ in age (AD: 70.0 years, SD, 9.3; control: 65.9 years, SD, 8.5; $P > .05$) or educational attainment (AD: 11.1 years, SD, 4.1; control: 11.9 years, SD, 2.8; $P > .3$).

Procedure

The Western Aphasia Battery (WAB),[44] Raven's Coloured Progressive Matrices,[45] Wechsler Adult Intelligence Scale-Revised,[46] Wechsler Memory Scale,[47] and Dementia Rating Scale[43] were administered to all patients with AD at the time of their initial referral by a neurologist for neuropsychologic assessment (test 1). The WAB drawing subtest was administered by asking each patient to draw spontaneously (not copy) a circle, cube, square, clock, tree, house, and person, after being shown a sample drawing for 10 seconds, as specified in the WAB instructions. Control subjects performed the same subtest. As part of an ongoing study, patients with AD have been retested at yearly intervals, wherever possible. Retesting always includes the WAB. Twenty-seven patients have been retested at 1 year, 14 of those at 2 years, and six again at 3 years. Disease duration at the time of initial testing was estimated by history from the patient, his family, and his medical record. All patients with AD underwent computed tomographic and 26 also underwent magnetic resonance imaging scans.

Each set of seven drawings from a single WAB session was assigned a random number and identifying data were masked. Drawings were then scored independently by two raters (one a physician, one with no training in medicine or psychology) who did not know whether a given drawing had been produced by a patient with AD or by a control subject or whether a drawing resulted from an initial assessment or from a retest. Raters analyzed drawings according to the criteria shown in Table 1; each drawing was rated individually unless otherwise stated. High interobserver agreement has previously been demonstrated for this scoring system.[22] For each item in Table 1, scores from the seven individual drawings were added to give a series of total item scores for each testing session. The mean of the two raters' scores became each subject's final score for each item for each testing session. Reliability of the ratings (as assessed by Pearson Product-Moment correlation coefficients between the two raters' scores for each item in Table 1, corrected by the Spearman-Brown formula, since final scores were means of two raters' scores) was acceptable. The mean reliability coefficient for the items in Table 1 was 0.79.

Because multiple comparisons were performed, $P < .005$ was used as a conservative criterion of significance for each statistical comparison.

RESULTS

At test 1, in the patients with AD, mean disease duration was 29.0 months (SD, 18.1). Their mean WAB aphasia quotient was 86.0 (SD, 10.8); Wechsler Adult Intelligence Scale-Re-

Table 2.—Mean Drawing Scores for Control Subjects and Patients With Probable Alzheimer's Disease (AD) With Student's *t* Test Significance of Difference*

	Control Subjects, Score (SD)	AD, Score (SD)	*P*
Overlap	0.04 (0.14)	0.05 (0.23)	NS
Orientation	0.96 (1.97)	0.92 (2.07)	NS
Details externalized	0.35 (1.92)	1.16 (2.96)	NS
Percentage right angles	26.15 (16.43)	28.97 (17.04)	NS
Percentage acute angles	39.96 (10.49)	39.70 (11.51)	NS
Percentage obtuse angles	33.23 (8.58)	31.35 (13.30)	NS
Redrawn lines	4.01 (4.39)	3.95 (3.72)	NS
Line production	14.08 (2.16)	13.30 (4.20)	NS
Line joining	12.13 (8.48)	11.24 (9.31)	NS
Line crossing	7.61 (4.28)	6.96 (3.80)	NS
Extras	0.23 (0.40)	0.41 (1.02)	NS
Angle production	0.88 (1.20)	0.64 (0.85)	NS
Neglect	0.01 (0.31)	0.09 (0.49)	NS
Displacement	−0.24 (0.46)	−0.24 (0.59)	NS
Details	37.13 (47.57)	23.20 (11.29)	NS
Perseveration	0.87 (0.98)	1.30 (1.72)	NS
Tremor	2.22 (3.28)	2.67 (2.78)	NS
Spatial relations	1.00 (1.23)	2.29 (2.49)	<.005
Total No. of angles	28.33 (5.06)	23.26 (8.59)	<.002
Perspective	2.17 (1.82)	3.80 (1.93)	<.0005
Simplification	1.77 (1.68)	4.58 (4.22)	<.0005
Overall impairment	5.20 (3.25)	9.34 (4.49)	<.0005

*NS indicates not significant.

vised verbal IQ, 83.5 (SD, 12.6); performance IQ, 79.7 (SD, 13.4); full scale IQ, 81.0 (SD, 12.7); Dementia Rating Scale total score, 99.6 (SD, 20.0); and Wechsler Memory Scale memory quotient, 75.4 (SD, 14.6). Table 2 summarizes subjects' drawing scores. It can be seen that patients with AD included significantly fewer angles and that they showed more impairment of perspective and spatial relations, more simplification, and more overall impairment.

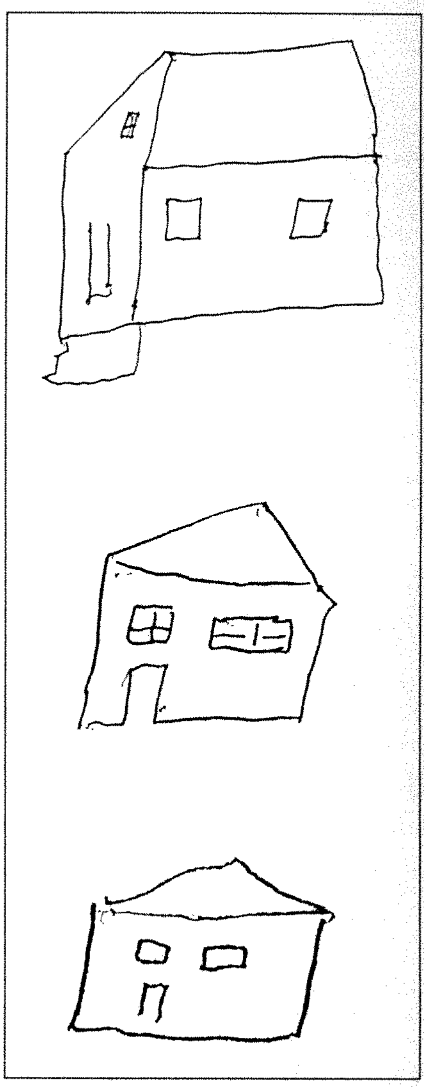
The Pearson Product-Moment correlation coefficients between overall drawing impairment and each of the WAB language scores (information content, fluency, comprehension, repetition, naming, and aphasia quotient) were all nonsignificant. There were also no significant correlations between overall drawing impairment and any of the Wechsler Memory Scale memory scores, including memory quotient. The WAB subtests significantly correlated with overall drawing impairment were reading ($r = -.64$; $P < .001$), writing ($r = -.62$; $P < .001$), and praxis ($r = -.50$; $P < .001$). The significant correlations of drawing impairment with Wechsler Adult Intelligence Scale-Revised IQs or subtest scores were with arithmetic ($r = -.58$; $P < .001$), picture arrangement ($r = -.59$; $P < .001$), block design ($r = -.64$; $P < .001$), and object assembly ($r = -.67$; $P < .001$). The only Dementia Rating Scale score significantly correlated with drawing impairment was construction ($r = -.53$; $P < .001$). Overall drawing impairment also correlated significantly with score on Raven's Coloured Progressive Matrices ($r = -.59$; $P < .001$).

Table 3.—Pearson Product-Moment Correlation Coefficients (*r*) Between Drawing Scores and Disease Duration Since Initial Testing

	r	*P*
Spatial relations	.20	>.1
Perspective	−.27	<.01
Simplification	−.30	<.01
Overall impairment	−.32	<.01
Total No. of angles	−.43	<.001

None of the drawing scores of either patients with AD or control subjects were significantly correlated with age.

To study how drawing deteriorates as AD progresses, we examined the correlations between the significantly impaired drawing item scores from Table 1 (simplification, perspective, total number of angles, spatial relations, and overall impairment) and disease duration since the first test. These retest results are shown in Table 3 and a typical example of drawing deterioration over three yearly tests is shown in the Figure.



Top, Drawing of a house by a 69-year-old woman with probable Alzheimer's disease of 2 years' estimated duration. Note poor perspective and mild difficulty with spatial relations between components. Middle, Drawing by same patient, 1 year later. Note simplification and lack of perspective. Bottom, Drawing by same patient, disease duration now 4 years. Note further simplification.

COMMENT

Table 2 shows that drawings of patients with AD are worse than drawings of control subjects in several respects. Simplification and a reduced number of angles (without alteration in the proportions of each type of angle) are characteristics shared between patients with AD and patients with LBD.[22] Impairment of spatial relations, also found in drawings of patients with AD, is a fundamental RBD deficit.[7,9,13,22,31-33] Impaired perspective is a fault shared by AD, LBD, and RBD.[22] Thus, drawings of patients with AD appear to be affected by deficiencies typical of both left- *and* right-hemisphere damage. There are some important, and not unanticipated, exceptions to this general rule. Constructions by patients with AD do not display the hemispatial neglect typical of RBD drawings. This finding is consistent with the usual bilateral and insidious nature of AD. Neglect generally recovers substantially after acute unilateral lesions and is unusual in degenerative diseases, even those, such as hemiparkinsonism, in which structures important in attention may be affected asymmetrically.[48-50] Lack of neglect in AD drawing attests to the brain's ability to compensate for slowly progressive damage to attention and intention systems, and particularly to the relative symmetry of the disease in question.

Unlike LBD drawings, AD drawings are not more tremulous than control subjects' drawings. However, LBD tremulousness is a feature closely linked to severity of right hemiparesis,[22] not a characteristic of AD.

Perseveration has been found to be a deficit common to both LBD and RBD drawings[22] but is not seen in the current series of patients with AD. Although perseveration is considered common in AD,[51] there are several potential explanations for our result. First, the overwhelming tendency of patients with AD to simplify their drawings may outweigh any propensity to perseverate. Second, it is verbal rather than nonverbal perseveration that has been found to be most typical of AD.[52,53] Third, even verbal perseverations are an infrequent phenomenon in the individual patient[52] and our brief drawing test may not have been extensive enough to bring out instances of perseverative behavior. Finally, because of the nature of the task, our techniques are more sensitive to *recurrent*, than to *stuck-in-set* or *continuous* perseveration,[51,54] which could potentially occur independently in the nonverbal behavior of patients with AD or at different times in disease progression.

It should be borne in mind that test 1 represents the first neuropsychologic assessment of the patients with AD. Thus, this group with early AD is likely to show less drawing impairment than would a group of patients with advanced disease.

Although some previous data[27] seem to suggest that drawing is worse with diffuse than with unilateral disease, direct quantitative comparison of drawing deficit severity between AD, RBD, and LBD would provide little useful information. Lesion size, useful in ensuring uniformity between LBD and RBD, is meaningless as a control in AD as drawing quality depends on the advance of the disease.

We found overall drawing impairment related to performance in several other areas. The Dementia Rating Scale construction, Wechsler Adult Intelligence Scale-Revised picture arrangement, block design, and object assembly clearly share with drawing underlying cognitive and motor processes in the visuospatial domain. Reading and Raven's Coloured Progressive Matrices, both of which require considerable visuoperceptual ability; writing, which makes demands on graphomotor executive function; and praxis, another executive ability, are all significantly correlated with the degree of drawing impairment in AD. This relationship with both perceptual and executive abilities implies that drawing disability in patients with AD, displaying characteristics typical of both RBD and LBD drawing, may reflect the presence of both a receptive and an executive visuospatial deficit (or dysfunction of a more basic cognitive mechanism common to both processes). To some extent a bitemporoparietal disease, AD is a disorder eminently capable of damaging both components of this dichotomy proposed by Duensing.[34]

Of even more interest than the significant correlations between drawing impairment and certain cognitive functions is the absence of a strong relationship between drawing and language or memory. Previous investigations of these interrelationships have proven inconclusive. Huff et al[55] described significant association between an overall constructional score and memory and language scores in AD. Henderson et al[4] found a significant relationship between drawing and naming but not between drawing and memory. On the other hand, Morris et al[56] identified, through factor analysis, three principal components explaining much of the variation in neuropsychological test performance in AD. These three factors, memory, language, and constructional performance, correspond to the three dissociated abilities in our study. Martin et al[39] found strong relationships between various constructional tasks and between various verbal tasks but little correlation across these groups. They used their finding of two distinct patterns of AD deficit as support for a *subgroup* rather than for a *stage* model for AD. Although our results must be interpreted in the light of this conflicting literature, they would also be more compatible with a subgroup model of AD. According to such a model, construction, language, and memory would be relatively distinct cognitive abilities, deficits of which coexist but do not necessarily develop in parallel in this degenerative disease. Stage and subgroup models are not mutually exclusive. It may be that specific abilities can be impaired relatively selectively early in the illness but that once a critical point is reached, global cognitive impairment must ensue.[41] It is worth noting that, in accord with this idea, the mean estimated disease duration is longer (63 months) in the study of Henderson et al,[4] which is more in keeping with a stage model, than in any of the cited investigations compatible with a subgroup model (52 months in the study of Morris et al[56]; 41 months in that of Martin et al[39]; 29 months in this study). Unfortunately, no estimate of duration is given in the study of Huff et al[55] supporting a stage model. Longitudinal studies, beginning early in the illness, and specifically addressed to these issues are likely to prove most fruitful in clarifying the temporal roles of these two models in AD.

From Table 3, it can be seen that, although AD drawing deficits worsen with time, the correlations are, for the most part, modest. Longitudinal behavioral studies of dementia[57,58] have described much variability in the rapidity of cognitive decline in AD, with deterioration occurring over several years. It is likely that more patients must be followed up longer than in our study to display more dramatic deteriorations in drawing quality.

Drawings of patients with AD display a combination of the deficits seen in both right- and left-hemisphere disease and our data suggest that both a perceptual and an executive visuospatial deficit are present. Severity of drawing impairment is relatively independent of severity of amnesia or language deficit.

Cognitive models of drawing, which may explain the associations and dissociations seen in patients with dementia and in those with focal lesions, need to be explored[59,60] and are likely to increase our understanding of the processes underlying normal drawing.

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References

1. Ajuriaguerra J, Muller M, Tissot R. A propos de quelques problèmes posés par l'apraxie dans les demences. *Encephale.* 1960;49:275-401.

2. Sjögren T, Sjögren H, Lindgren AGH. Morbus Alzheimer and morbus Pick. *Acta Psychiatr Neurol Scand.* 1952;82(suppl):1-152.

3. Perez FI, Rivera VM, Meyer JS, Gay JRA,

Taylor RL, Mathew NT. Analysis of intellectual and cognitive performance in patients with multi-infarct dementia, vertebrobasilar insufficiency with dementia, and Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 1975;38:533-540.

4. Henderson VW, Mack W, Williams BW. Spatial disorientation in Alzheimer's disease. *Arch Neurol.* 1989;46:391-394.

5. Buchner DM, Larson EB. Falls and fractures in patients with Alzheimer-type dementia. *JAMA.* 1987;257:1492-1495.

6. Piercy M, Hecaen H, Ajuriaguerra J. Constructional apraxia associated with unilateral cerebral lesions: left and right sided cases compared. *Brain.* 1960;83:225-245.

7. Arrigoni G, De Renzi E. Constructional apraxia and hemispheric locus of lesion. *Cortex.* 1964;1:170-197.

8. Warrington EK, James M, Kinsbourne M. Drawing disability in relation to laterality of cerebral lesion. *Brain.* 1966;89:53-82.

9. De Renzi E, Faglioni P. The relationship between visuospatial impairment and constructional apraxia. *Cortex.* 1967;3:327-342.

10. Benson DF, Barton MI. Disturbances in constructional ability. *Cortex.* 1970;6:19-46.

11. Hecaen H, Assal G. A comparison of constructive deficits following right and left hemispheric lesions. *Neuropsychologia.* 1970;8:289-303.

12. Dee HL. Visuoconstructive and visuoperceptual deficit in patients with unilateral cerebral lesions. *Neuropsychologia.* 1970;8:305-314.

13. Gainotti G, Tiacci C. Patterns of drawing disability in right and left hemispheric patients. *Neuropsychologia.* 1970;8:379-384.

14. Benton AL. Visuoconstructive disability in patients with cerebral disease: its relationship to side of lesion and aphasic disorder. *Doc Ophthalmol.* 1973;34:67-76.

15. Black FW, Strub RL. Constructional apraxia in patients with discrete missile wounds of the brain. *Cortex.* 1976;12:212-220.

16. Arena R, Gainotti G. Constructional apraxia and visuoperceptive disabilities in relation to laterality of cerebral lesions. *Cortex.* 1978; 14:463-473.

17. Mack JL, Levine RN. The basis of visual constructional disability in patients with unilateral cerebral lesions. *Cortex.* 1981;17:515-532.

18. Black RW, Bernard BA. Constructional apraxia as a function of lesion locus and size in patients with focal brain damage. *Cortex.* 1984;20:111-120.

19. Kimura D, Faust R. Spontaneous drawing in an unselected sample of patients with unilateral cerebral damage. In: Ottoson D, ed. *Duality and Unity of the Brain.* New York, NY: Macmillan Publishing Co Inc; 1987:114-146.

20. Stiles-Davis J, Janowsky J, Engel M, Nass R. Drawing ability in four young children with congenital unilateral brain lesions. *Neuropsychologia.* 1988;26:359-371.

21. Grossman M. Drawing deficits in brain-damaged patients' freehand pictures. *Brain Cogn.* 1988;8:189-205.

22. Kirk A, Kertesz A. Hemispheric contributions to drawing. *Neuropsychologia.* 1989;27:881-886.

23. Kleist K. Kriegsverletzungen des Gehirns. In: Schjerning O, ed. *Handbuch der arztlichen Erfahrungen im Weltkriege: 1914-1918.* Leipzig, Germany: Barth, 1922.

24. Lhermitte J, Trelles JO. Sur l'apraxie pure constructive. *Encephale.* 1933;28:413-444.

25. Mayer-Gross W. Some observations on apraxia. *Proc R Soc Med.* 1935;28:1203-1212.

26. Gainotti G. A quantitative study of the 'closing-in' symptom in normal children and in brain-damaged patients. *Neuropsychologia.* 1972;10:429-436.

27. Benton AL, Fogel ML. Three-dimensional constructional praxis. *Arch Neurol.* 1962;7:347-354.

28. Villa G, Gainotti G, De Bonis C. Constructive disabilities in focal brain-damaged patients: influence of hemispheric side, locus of lesion and coexistent mental deterioration. *Neuropsychologia.* 1986;24:497-510.

29. Friedland RP, Koss E, Haxby JV, et al. Alzheimer disease: clinical and biological heterogeneity. *Ann Intern Med.* 1988;109:298-311.

30. Paterson A, Zangwill OL. Disorders of visual space perception associated with lesions of the right cerebral hemisphere. *Brain.* 1944;67:331-358.

31. McFie J, Piercy MF, Zangwill OL. Visual-spatial agnosia associated with lesions of the right cerebral hemisphere. *Brain.* 1960;73:167-190.

32. Gainotti G, Messerli P, Tissot R. Troubles du dessin et lesions hèmisphèriques retrorolandiques unilaterales gauches et droites. *Encephale.* 1972;61:245-264.

33. Collignon R, Rondeaux J. Approche clinique des modalités de l'apraxie constructive secondaire aux lesions corticales hèmisphèriques gauches et droites. *Acta Neurol Belg.* 1974;74:137-146.

34. Duensing F. Raumagnostische und ideatorisch-apraktische storung des gestaltenden Handelns. *Dtsch Z Nervenheilkd.* 1953;170:72-94.

35. McFie J, Zangwill OL. Visual-constructive disabilities associated with lesions of the left cerebral hemisphere. *Brain.* 1960;83:243-260.

36. Gainotti G, Tiacci C. Sui rapporti fra aprassia costruttiva, agnosia visuospaziale e negligenze spaziale unilaterale. *Riv Patol Nerv Ment.* 1972;93:103-116.

37. Piercy MF, Smyth V. Right hemisphere dominance for certain non-verbal intellectual skills. *Brain.* 1962;85:775-790.

38. Rainville C, Cardu B. L'apraxie constructive dans la demence de type Alzheimer. Presented at the Canadian Congress of Neurological Sciences; June 1988; Quebec.

39. Martin A, Brouwers P, Lalonde F, Cox C, Teleska P, Fedio P. Towards a behavioral typology of Alzheimer's patients. *J Clin Exp Neuropsychol.* 1986;8:594-610.

40. Constantinidis J. Is Alzheimer's disease a major form of senile dementia? Clinical, anatomical, and genetic data. In: Katzman R, Terry RD, Bick KL, eds. *Alzheimer's Disease: A Report of Progress in Research.* New York, NY: Raven Press; 1978;19:15-25.

41. Adams RD, Victor M. *Principles of Neurology.* New York, NY: McGraw-Hill International Book Co; 1989:925-926.

42. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.

43. Mattis S. Mental status examination for organic mental syndrome in the elderly patients. In: Bellak L, Karasu TB, eds. *Geriatric Psychiatry.* New York, NY: Grune & Stratton; 1976.

44. Kertesz A. *The Western Aphasia Battery.* New York, NY: Grune & Stratton; 1982.

45. Raven JC. *Guide to Using the Coloured Progressive Matrices.* London, England: Lewis; 1965.

46. Wechsler D. *Wechsler Adult Intelligence Scale-Revised.* New York, NY: Harcourt Brace Jovanovich; 1981.

47. Wechsler D. A standardized memory scale for clinical use. *J Psychol.* 1945;19:87-95.

48. Martinez AJ, Utterback RA. Unilateral Parkinson's disease: clinical and neuropathologic findings: a case report. *Neurology.* 1973;23:164-170.

49. Ljungberg T, Ungerstedt U. Sensory inattention produced by 6-hydroxydopamine-induced degeneration of ascending dopamine neurons in the brain. *Exp Neurol.* 1976;53:585-600.

50. Blonder LX, Gur RE, Gur RC, Saykin AJ, Hurtig HI. Neuropsychological functioning in hemiparkinsonism. *Brain Cogn.* 1989;9:244-257.

51. Sandson J, Albert ML. Varieties of perseveration. *Neuropsychologia.* 1984;22:715-732.

52. Fuld PA, Katzman R, Davies P. Intrusions as a sign of Alzheimer dementia: chemical and pathological verification. *Ann Neurol.* 1982; 11:155-159.

53. Bayles KA, Tomoeda CK, Kaszniak AW. Verbal perseveration of dementia patients. *Brain Lang.* 1985;25:102-116.

54. Sandson J, Albert ML. Perseveration in behavioral neurology. *Neurology.* 1987;37:1736-1741.

55. Huff FJ, Becker JT, Belle SH, Nebes RD, Holland AL, Boller F. Cognitive deficits and clinical diagnosis of Alzheimer's disease. *Neurology.* 1987;37:1119-1124.

56. Morris JC, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD), I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989;39:1159-1165.

57. Botwinick J, Storandt M, Berg L, Boland S. Senile dementia of the Alzheimer type: subject attrition and testability in research. *Arch Neurol.* 1988;45:493-496.

58. Berg L, Miller JP, Storandt M, et al. Mild senile dementia of the Alzheimer type, II: longitudinal assessment. *Ann Neurol.* 1988;23:477-484.

59. Delis DC, Kiefner MG, Fridlund AJ. Visuospatial dysfunction following unilateral brain damage: dissociations in hierarchical and hemispatial analysis. *J Clin Exp Neuropsychol.* 1988;10:421-431.

60. Grossi D, Orsini A, Modafferi A, Liotti M. Visuoimaginal constructional apraxia: on a case of selective deficit of imagery. *Brain Cogn.* 1986;5:255-267.

Reduces levodopa/ carbidopa dosage — *usually by 10–30%[2,4†]*

Favorable safety profile — *lowering levodopa/carbidopa dose reduces side effects[2,3]*

Selectively inhibits MAO-B *to conserve endogenous and exogenous dopamine[1-3]*

Stabilizes the clinical course — *71% of patients improved[3]*

Improved walking, dressing; reduced drooling and tremor[2]

No tyramine ("cheese") effect *at recommended dosages**

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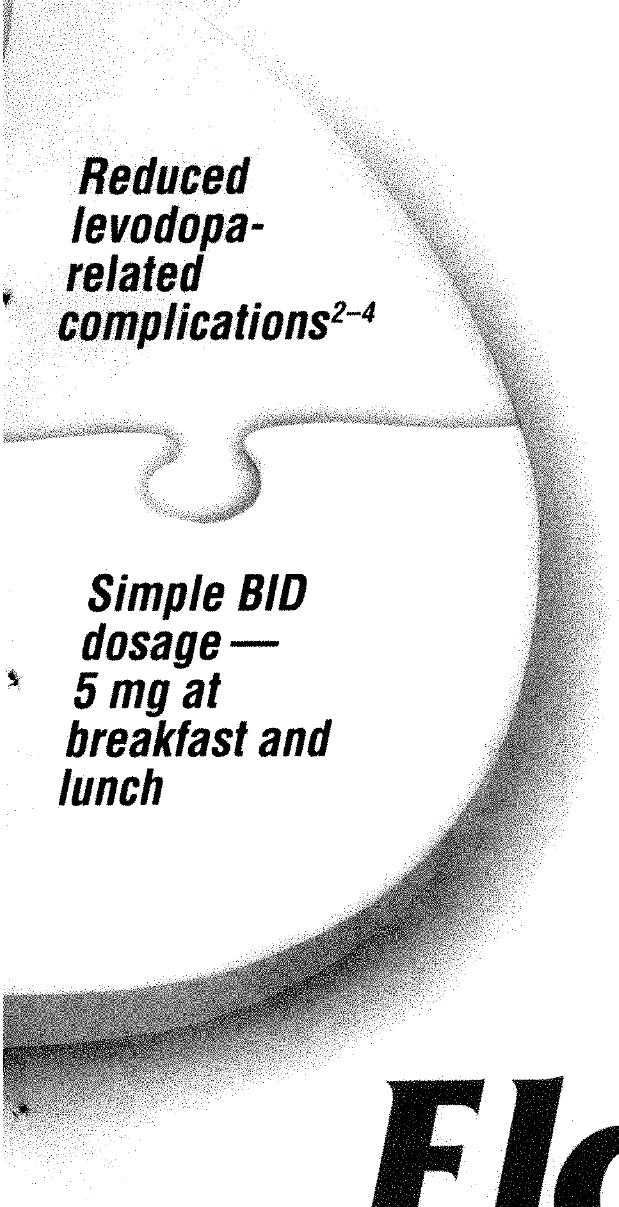
Reduced levodopa-related complications[2-4]
Simple BID dosage — 5 mg at breakfast and lunch

Management of Parkinson's disease...
still a puzzle

Benefits that provide a fitting solution

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

Fits your therapeutic strategy

*Higher doses have not been shown to increase benefit and have increased the risk of side effects. Please see Dosage and Administration section of prescribing information.

†Further reduction of levodopa/carbidopa may be possible during continued selegiline therapy.

See next page for brief summary of prescribing information.

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

BRIEF SUMMARY

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

INDICATIONS AND USAGE:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated in patients with a known hypersensitivity to this drug.

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Because of reports of fatal interactions, MAOIs are ordinarily contraindicated for use with meperidine (DEMEROL & other tradenames). This warning is often extended to other opioids. Because the mechanism of interaction between MAOIs and meperidine is unknown, it seems prudent, in general, to avoid this combination.

Definitive clinical data on the concomitant use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) and fluoxetine hydrochloride (PROZAC) is not available. Death has been reported to occur following the initiation of therapy with nonselective MAOI's (NARDIL, PARNATE) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with ELDEPRYL® (SELEGILINE HYDROCHLORIDE), however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately 5 half-lives) should elapse beweeen discontinuation of fluoxetine and initiation of MAOI therapy. Based on experience with the combined use of MAOI's and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with fluoxetine.

PRECAUTIONS:

General: Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients: Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests: No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL® (SELEGILINE HYDROCHLORIDE). Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions: No interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (See WARNINGS and PRECAUTIONS.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: *Pregnancy Category C.* Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use: The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction: The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with ELDEPRYL® (SELEGILINE HYDROCHLORIDE) obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM: Dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE: Slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES: Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

MISCELLANEOUS: Asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE).

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N = 49	placebo N = 50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

OVERDOSAGE:

Selegiline: No specific information is available about clinically significant overdoses with ELDEPRYL® (SELEGILINE HYDROCHLORIDE). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors (e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)).

Overdose with Non-Selective MAO Inhibition: NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

(AUGUST, 1990 011-25-P-103)

References:

1. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science.* 1989;245:519–522.
2. Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clin Neuropharmacol.* 1988;11(1):45–55.
3. Lieberman AN, Gopinathan G, Neophytides A, et al. Deprenyl versus placebo in Parkinson's disease: A double-blind study. *NY State J Med.* 1987;87:646–649.
4. Presthus J, Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. *Acta Neurol Scand.* 1983;95(suppl):127–133.

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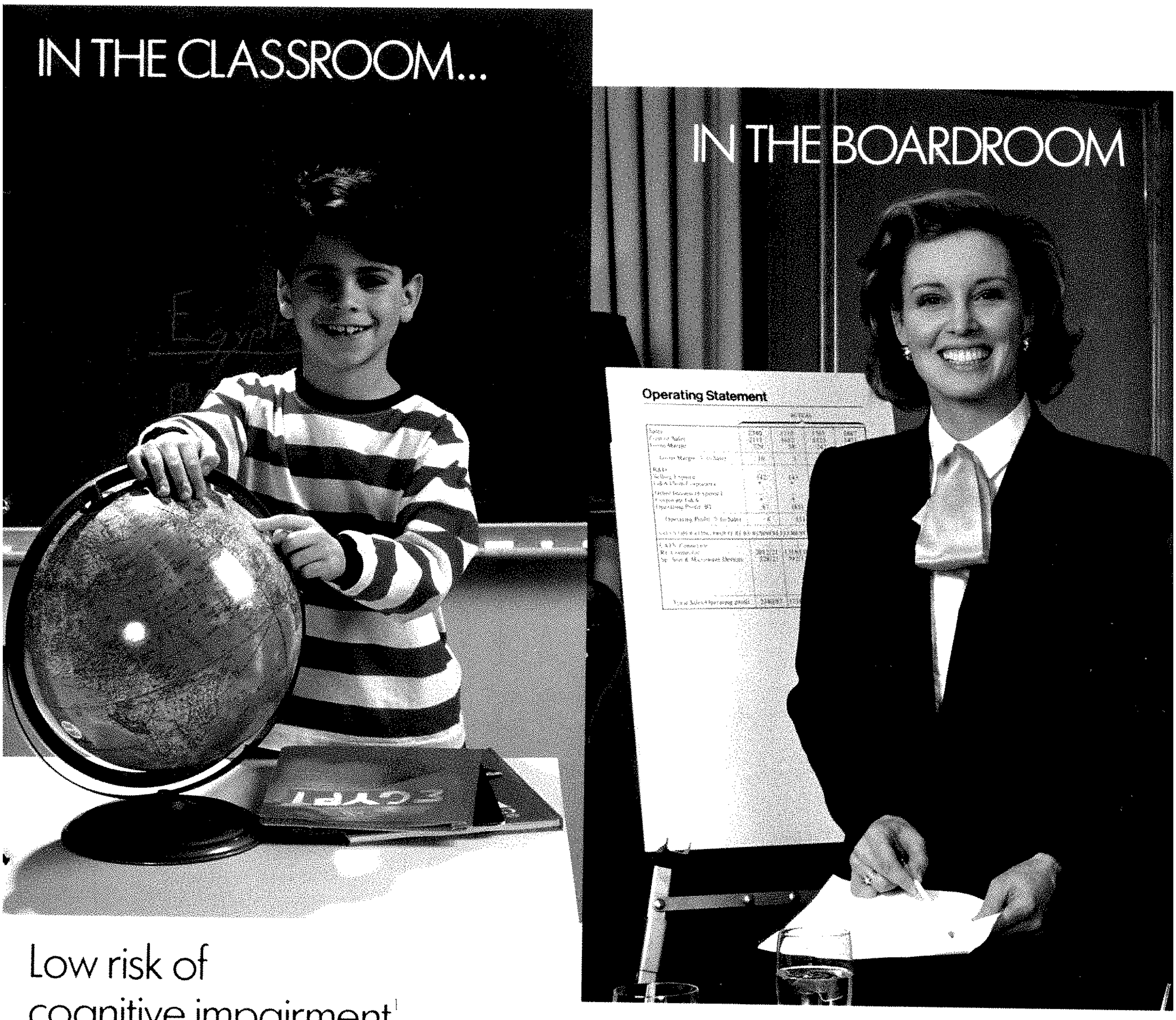
Seizures controlled, thoughts clear, smiles bright



Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

CIBA–GEIGY

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Tegretol®

200 mg scored tablets
100 mg chewable tablets

carbamazepine USP

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References

1 Smith DB, Mattson RH, Cramer JA et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone *Epilepsia* 1987;28(suppl 3):S50-S58

2 Mattson RH, Cramer JA, Collins JF et al Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med* 1985;313:145-151

3 Herranz JL, Armijo JA, Arteaga R Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children *Epilepsia* 1988;29:794-804

Tegretol®

carbamazepine USP

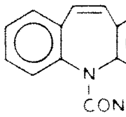
Chewable Tablets of 100 mg—red-speckled, pink   Tablets of 200 mg—pink

> WARNING
>
> APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA
>
> ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS
>
> BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27

Inactive Ingredients Colloidal silicon dioxide, FD&C Red No 3 (chewable tablets only), FD&C Red No 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only) starch stearic acid, and sucrose (chewable tablets only)

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia The mechanism of action remains unknown

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets Tegretol in blood is 76% bound to plasma proteins Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug Usual adult therapeutic levels are between 4 and 12 μg/ml Following oral administration, serum levels peak at 4 to 5 hours The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses Tegretol is metabolized in the liver After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types

1 Partial seizures with complex symptomatology (psychomotor, temporal lobe) Patients with these seizures appear to show greater improvement than those with other types

2 Generalized tonic-clonic seizures (grand mal)

3 Mixed seizure patterns which include the above, or other partial or generalized seizures

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General)

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia

Beneficial results have also been reported in glossopharyngeal neuralgia

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline etc Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol These reactions have been extremely rare However, a few fatalities have been reported

Tegretol has shown mild anticholinergic activity, therefore, patients with increased intraocular pressure should be closely observed during therapy

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE)

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance In addition measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used

Thyroid function tests have been reported to show decreased values with Tegretol administered alone

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected

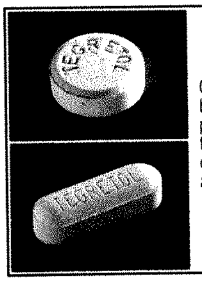
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1, talipes 1, anophthalmos, 2) In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy Therefore, monotherapy is recommended for pregnant women



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

Hemopoietic System Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria

Skin Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis In certain cases, discontinuation of therapy may be necessary

Cardiovascular System Congestive heart failure, edema aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy

Some of these cardiovascular complications have resulted in fatalities Myocardial infarction has been associated with other tricyclic compounds

Liver Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis

Respiratory System Pulmonary hypersensitivity characterized by fever dyspnea, pneumonitis or pneumonia

Genitourinary System Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher Relevance of these findings to humans is unknown

Nervous System Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations transient diplopia oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established

Digestive System Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis

Eyes Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes

Musculoskeletal System Aching joints and muscles, and leg cramps

Metabolism Fever and chills Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported Cases of frank water intoxication with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS Laboratory Tests)

Other Isolated cases of a lupus erythematosus-like syndrome have been reported There have been occasional reports of elevated levels of cholesterol HDL cholesterol and triglycerides in patients taking anticonvulsants

A case of aseptic meningitis accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose adults >60 g (39-year-old man) Highest known doses survived adults, 30 g (31-year-old woman), children, 10 g (6-year-old boy), small children 5 g (3-year-old girl)

Oral LD_{50} in animals (mg/kg) mice, 1100-3750, rats, 3850-4025 rabbits, 1500-2680, guinea pigs 920

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours Neuromuscular disturbances are the most prominent Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested

Respiration Irregular breathing, respiratory depression

Cardiovascular System Tachycardia hypotension or hypertension, shock conduction disorders

Nervous System and Muscles Impairment of consciousness ranging in severity to deep coma Convulsions, especially in small children Motor restlessness, muscular twitching, tremor, athetoid movements opisthotonos, ataxia, drowsiness dizziness mydriasis, nystagmus, adiadochokinesia ballism psychomotor disturbances, dysmetria Initial hyperreflexia, followed by hyporeflexia

Gastrointestinal Tract Nausea, vomiting

Kidneys and Bladder Anuria or oliguria, urinary retention

Laboratory Findings Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria EEG may show dysrhythmias

Combined Poisoning When alcohol, tricyclic antidepressants barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded There is no specific antidote

Elimination of the Drug. Induction of vomiting

Gastric lavage Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol

Measures to Reduce Absorption Activated charcoal, laxatives

Measures to Accelerate Elimination Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure Replacement transfusion is indicated in severe poisoning in small children

Respiratory Depression Keep the airways free, resort, if necessary, to endotracheal intubation, artificial respiration and administration of oxygen

Hypotension, Shock Keep the patient's legs raised and administer a plasma expander If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered

Convulsions Diazepam or barbiturates

Warning Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma However barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week)

Surveillance Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days

Treatment of Blood Count Abnormalities If evidence of significant bone marrow depression develops, the following recommendations are suggested (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery

Special periodic studies might be helpful as follows (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests) Dosage should be adjusted to the needs of the individual patient A low initial daily dosage with a gradual increase is advised As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level Tablets should be taken with meals

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b i d Increase at weekly intervals by adding up to 200 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age Doses up to 1600 mg daily have been used in adults in rare instances ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily

Children 6-12 years of age—Initial: 100 mg b i d Increase at weekly intervals by adding 100 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily

Combination Therapy: Tegretol may be used alone or with other anticonvulsants When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C)

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b i d on the first day for a total daily dose of 200 mg This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain Do not exceed 1200 mg daily

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily However, some patients may be maintained on as little as 200 mg daily while others may require as much as 1200 mg daily At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet

Protect from moisture

Dispense in tight container (USP)

Also available as Tegretol suspension 100 mg/5 ml, in 450 ml bottles

Printed in U S A   C90-34 (Rev 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

A Trial of Thiamine in Alzheimer's Disease

K. A. Nolan, PhD; R. S. Black, MD; K. F. R. Sheu, PhD; J. Langberg; J. P. Blass, MD, PhD

• Because a previous short-term study demonstrated a statistically significant, but not clinically important, improvement in cognitive test scores during thiamine treatment in patients with dementia of the Alzheimer's type, a 12-month, double-blind, parallel-group study was conducted to examine whether long-term administration of thiamine at 3 g/d might slow the progression of dementia of the Alzheimer's type. Fifteen subjects were enrolled and 10 completed the 1-year study. Data are available for two additional subjects through the first 9 months of study. No significant differences were found between the placebo and thiamine groups at any point during the study. In both groups, overall means for the Mini-Mental State Examination, verbal learning, and naming scores decreased significantly over the 12-month study period. These results do not support the hypothesis that long-term administration of thiamine at 3 g/d might slow the progression of dementia of the Alzheimer's type.

(*Arch Neurol.* 1991;48:81-83)

Biochemical abnormalities in thiamine-dependent enzymes in brains and other tissues in patients with dementia of the Alzheimer's type (DAT) have been described elsewhere.[1,2] The activities of thiamine-dependent enzymes in the brains of patients with DAT appear to be decreased to a greater extent than the "nonspecific" reductions in a number of constituents that Bowen et al[3] related to brain atrophy. The reductions are comparable to the "specific" deficits in the cholinergic marker enzyme, choline acetyltransferase.[3] The fact that the decreases in the activities of thiamine-dependent enzymes also occurred in areas of the brain that were histologically relatively unaffected suggests that they are not nonspecific results of tissue damage. Subtle abnormalities in one of these enzymes, transketolase, were also identified in red blood cells and in cultured skin fibroblasts from patients with Alzheimer's disease.[1,2]

A previously published study by Blass et al[4] was designed to test the potential relationship of these observations to the disease process. The results of that study, in which thiamine (vitamin B_1) was administered to patients with DAT at a dose of 3 g/d for 3 months, demonstrated a statistically significant improvement on cognitive testing during the treatment period relative to a comparable placebo period. In this double-blind, placebo-controlled crossover study, each patient received either placebo or thiamine at a dose of 3g/d for 3 months, followed by 3 months of the alternate treatment. Efficacy measures were the Mini-Mental State Examination (MMSE),[5] the dementia rating scale of Blessed et al,[6] and the caregiver-scored Haycox behavioral scale.[7] Mean MMSE scores during treatment with thiamine were significantly higher than MMSE scores during the placebo period, although there was no significant difference observed in scores on either of the behavioral rating scales. Moreover, the thiamine-placebo difference in MMSE scores was small (mean difference, 0.72 ± 0.14).

Although the short-term effect of thiamine was not clinically important, if this small increment in MMSE score could be maintained over longer periods, the overall effect might be to slow the rate of deterioration of cognitive functioning in DAT. A double-blind, placebo-controlled, parallel-group study was undertaken to test this hypothesis. Because no effect of thiamine on behavioral ratings was shown in the first study,[4] efficacy measures were limited to tests of cognitive function.

PATIENTS AND METHODS

Patients

Patients were recruited from the Geriatric Evaluation Service of the Burke Rehabilitation Center, White Plains, NY, a subspecialty clinic that has been described in detail.[8] Each patient recruited for the study had the clinical diagnosis of either probable or possible Alzheimer's disease, by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Diseases Association criteria[9]; of the 15 patients enrolled in the study, 13 carried a diagnosis of probable Alzheimer's disease and two a diagnosis of possible Alzheimer's disease. Five patients were male, and 10 were female. The patients ranged in age from 59 to 87 years, with a mean age of 76.3 years. At entry, their scores on the MMSE[5] ranged from 8 to 23, with a mean of 16.4. None of the subjects in this study had participated in the previous study of thiamine in DAT. Prior to enrollment, written informed consent was obtained from the patient and from the responsible caregiver.

Ten subjects completed the 1-year study. Two subjects were withdrawn from the study after 3 months or less for lack of compliance. Two other subjects were unavailable for examination at 12 months because of unrelated health problems (their own or a caregiver's). Dropouts and subjects without observations at study completion were evenly distributed across treatment groups. The data from one additional subject had to be eliminated from analyses because of a clerical error that resulted in the patient being given both placebo and thiamine at different times. Characteristics of the 12 patients who completed at least the first 9 months of study and whose data were included in the final analyses are given in Table 1.

Medications

Thiamine hydrochloride and lactose were obtained from a drug manufacturer (Commons Brothers Inc, Elmsford, NY) and were formulated as capsules by staff pharmacists at the Burke Rehabilitation Center. Capsules contained either 1 g of thiamine, made up with lactose excipient, or a lactose

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Reprint requests to Dementia Research Service, Burke Rehabilitation Center, 785 Mamaroneck Ave, White Plains, NY 10605 (Dr Nolan).

Table 1.—Subject Characteristics*

Patient No./Sex/Age, y	MMSE at Entry	Diagnosis
1/F/59	20†	Probable AD
2/F/76	17	Probable AD
3/F/76	21	Probable AD
4/M/87	9	Possible AD
5/M/81	23	Probable AD
6/M/73	13	Probable AD
7/M/70	20	Probable AD
8/M/66	23	Probable AD
9/F/78	12	Probable AD
10/F/77	16	Probable AD
11/F/84	16†	Possible AD
12/F/73	9	Probable AD
13/F/86	19‡	Probable AD
14/F/84	8§	Probable AD
15/F/75	20§	Probable AD

*MMSE indicates Mini-Mental State Examination; and AD, Alzheimer's disease.
†Data available only through first 9 months of study.
‡Protocol violation.
§Completed 3 months of study or less.

Table 2.—Mini-Mental State Examination Scores for 10 Subjects Completing 12-Month Study*

		Intervals, mo			
	Baseline	3	6	9	12
Thiamine group (n = 5)	16.6 (5.73)	14.6 (7.02)	13.4 (7.2)	12.2 (8.07)	10.4 (9.13)
Placebo group (n = 5)	16.0 (5.7)	17.0 (6.56)	16.4 (7.7)	13.4 (6.43)	14.6 (7.09)
Overall	16.3 (5.4)	15.8 (6.53)	14.9 (7.2)	12.8 (6.91)	12.5 (8.02)

*Values are mean (± SD).

Table 3.—Analysis of Variance Summary for Mini-Mental State Examination Scores*

Source	Sum of Squares	df	Mean Square	F	P
Subjects/groups	10 454.58	1	10 454.58	44.23	.001
Group	52.02	1	52.02	.22	.651
Error	1890.80	8	236.35	...	...
Time	119.72	4	29.93	6.63	.001
Group × time	33.48	4	8.37	1.85	.143
Error	144.40	32	4.51	...	...

*Mini-Mental State Examination scores are given in Table 2.

placebo. Placebo capsules were indistinguishable from thiamine capsules in appearance, size, and weight.

Random assignment of patients to treatment groups was carried out by the pharmacy, where the only records of these assignments were maintained until the study was completed. Caregivers were instructed to have the patient take three capsules a day; patients assigned to the active medication group were receiving 3 g of thiamine a day.

At each clinic visit, subjects were given a 3-month supply of capsules. Study compliance was monitored by pill counts. All 12 subjects who continued taking thiamine beyond the first 3 months of the study had better than 80% compliance.

Procedures

Patients were seen at 3-month intervals. At each clinic visit, the physician performed a brief physical examination. The CERAD (consortium to *e*stablish a *r*egistry for *A*lzheimer's *d*isease) neuropsychological battery[10] was administered to each patient by the same examiner at each visit, including the baseline visit. This battery includes a verbal fluency (categories) measure, a short (15-item) version of the Boston Naming Test, the MMSE, and a constructional praxis test. In addition, there is a 10-item word list learning test and tests of delayed recall and recognition based on the same 10-word list. To avoid potential practice effects in the word list tests, four alternate 10-word lists were used, and an appropriate set of distractors was chosen for each list for the recognition test. The order of presentation of the lists was counterbalanced across subjects, with the constraint that the CERAD list be used for baseline and 12-month evaluations, as required by the CERAD protocol. The MMSE was defined a priori as the primary efficacy measure.

RESULTS

Data from the 10 subjects who completed the full 12 months of study are reported first. As shown in Table 2, subjects assigned to the thiamine and placebo groups were roughly equivalent in terms of MMSE scores at baseline (means of 16.6 and 16.0, respectively). A 2-way (group × time) repeated analysis of variance measures applied to MMSE scores obtained at the five clinic visits (at baseline and at months 3, 6, 9, and 12) (Table 3) indicated no significant difference between the treatment groups ($F_{1,8} = .334$). There is a significant effect of time ($F_{4,32} = 7.866$, $P < .001$), with mean MMSE scores decreasing from 16.3 to 12.5 over the 12-month study period. The Newman-Keuls procedure for tests on the difference between all possible pairs of means was applied to the overall MMSE means. The mean MMSE scores at months 6, 9, and 12 were significantly ($P < .05$) lower than those at baseline. The mean MMSE scores at month 12 were significantly lower than those at all other observations, and mean scores at month 9 were lower than those at all earlier observations. The mean MMSE scores at month 6 were lower than those at baseline. No other differences were significant at the .05 level for the Newman-Keuls tests. The group × time interaction was not significant ($F_{4,32} = 1.603$, $P = .221$).

Scores on the secondary efficacy measures (verbal fluency, naming, constructional praxis, verbal learning, and delayed recognition) were also subjected to two-way (group × time) repeated analyses of variance measures. Delayed recognition performance was expressed as a', a function of hit rate and false-alarm rate. There was no significant difference between the thiamine and placebo groups, and no significant group × time interaction on any of these measures. In the analysis of verbal learning scores, the effect of time was significant ($F_{4,32} = 4.03$, $P = .018$), with the means at month 12 significantly ($P < .05$) lower than those at baseline and month 3 by Newman-Keuls. The effect of time was also significant in naming ($F_{4,32} = 3.047$, $P = .047$), with scores at month 12 significantly ($P < .05$) lower than those at all earlier observations. Mean naming scores at month 6 were also significantly lower than those at month 3 and at baseline. Delayed recall scores were not formally analyzed, due to floor effects; only three of the 10 subjects were ever able to recall more than one item from the 10-word lists, and the most frequent delayed recall score was 0.

Two-way (group × time) repeated analyses of variance measures were also applied to the data for all 12 subjects (six in each group) who completed the first 9 months of the study. As above, the effect of time on MMSE scores was significant ($F_{3,30} = 9.38$, $P < .001$), with the mean MMSE scores at month 9 significantly lower ($P < .05$ by Newman-Keuls) than those at all earlier observations. The effect of time on verbal learning scores was also significant ($F_{3,30} = 5.88$, $P = .003$) and, again, the mean scores at month 9 were significantly lower than those at all earlier observations. There were neither significant treatment group effects nor any significant group × time interactions.

COMMENT

The results of this double-blind, placebo-controlled, parallel-group study do not support the hypothesis that thiamine either improves cognition or slows the progression of cognitive deterioration in patients with DAT. The average MMSE decrement of 3.8 points over a 1-year period observed in these patients is consistent with other published data.[11] However, it must be noted that the rate of change in MMSE scores varied greatly among patients, with two patients, both of whom were in the placebo group, showing no decrement in MMSE scores from baseline to month 12, while other patients lost as many as 12 MMSE points over the same period.

Although these negative results are based on relatively small samples (10 subjects over 12 months, and 12 subjects over 9 months), the positive results obtained by Blass et al[4] were based on an equally small sample (11 subjects). In addition, the absence of a significant effect of thiamine in this study is not a matter of there being a small, but statistically insignificant, difference between the two groups in the predicted direction. On the contrary, the tendency was for more rapid deterioration in the thiamine-treated group than in the placebo group.

The inclusion of other secondary efficacy measures was intended to increase sensitivity to effects in specific areas of cognition that might not be detected by a single, global measure of cognition, such as the MMSE. If, for example, thiamine were effective in improving constructional praxis, the one-point difference in MMSE score that could result from such improvement would be difficult to detect. The use of the CERAD neuropsychological battery provided more detailed evaluations of several specific cognitive domains, including verbal fluency, naming, constructional praxis, and verbal learning. The fact that MMSE scores, verbal learning scores, and naming scores were seen to decrease significantly over time confirms that these measures are sufficiently sensitive to changes in ability in these domains. The absence of significant effects of thiamine is, within at least these three tests, not likely to be due to lack of sensitivity in the outcome measures.

Because this study employed a parallel-group design, as opposed to the cross-over design used in the previous study, it constitutes a more conservative test of the effect of thiamine on cognition in DAT. The previous study examined the effect of short-term administration of thiamine, and the magnitude of the effect in that study was very small (1.3 points on the MMSE). Cross-over studies are less appropriate for the investigation of long-term effects and are subject to carry-over effects and order effects.[12] In a study of long-term effects, such as this one, and especially when maturational factors are expected to come into play, as in progressive dementia, a parallel-group design yields a straightforward interpretation of the results. These results do not support the hypothesis that a 3-g/d dose of thiamine is effective in slowing cognitive deterioration in DAT.

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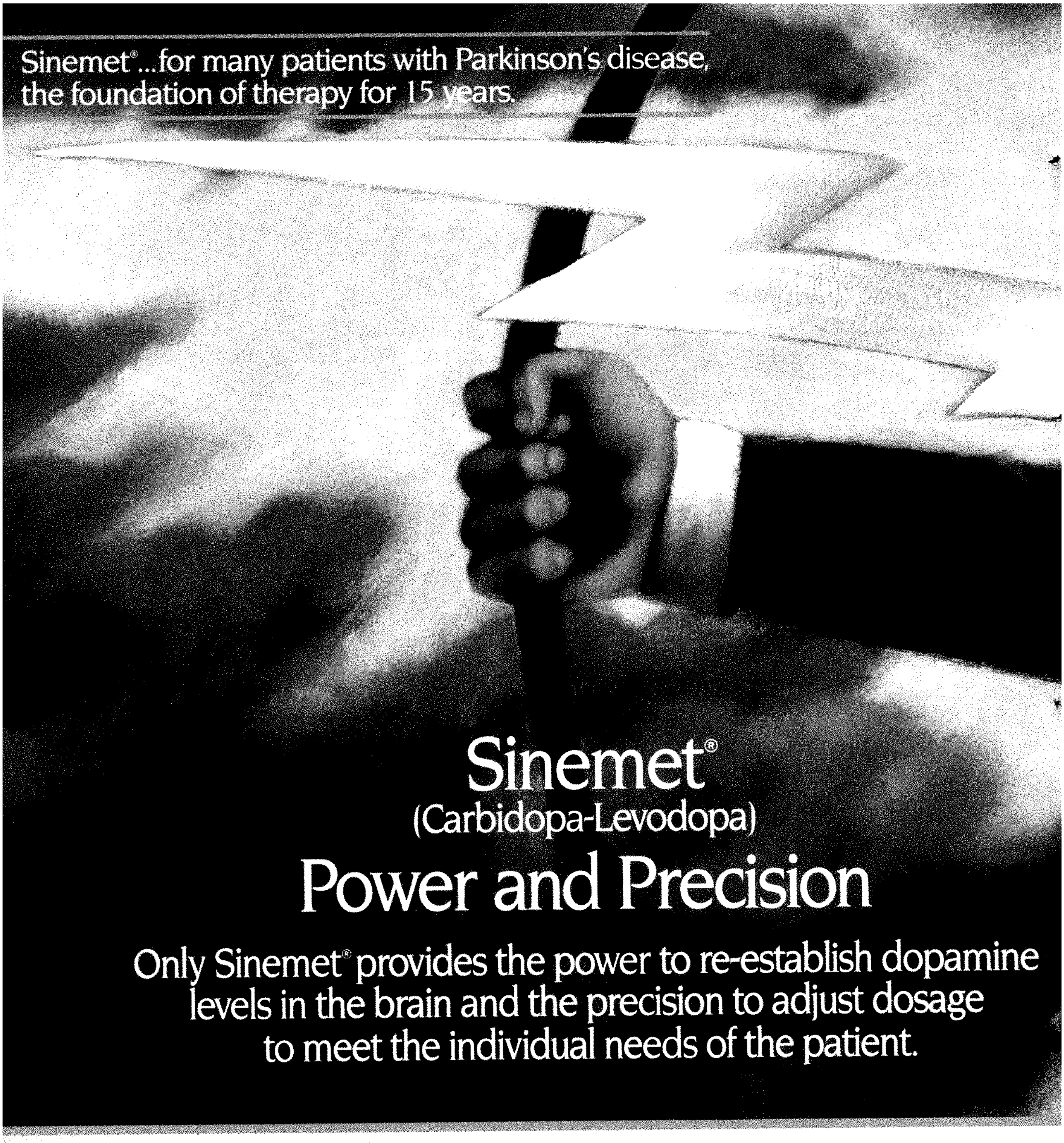
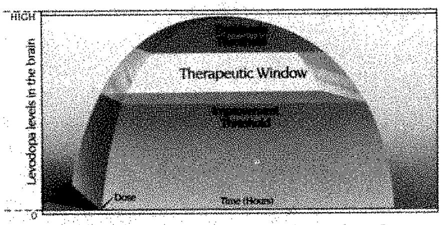
References

1. Gibson GE, Sheu KFR, Blass JP, et al. Reduced activities of thiamine-dependent enzymes in the brains and peripheral tissues of patients with Alzheimer's disease. *Arch Neurol.* 1988;45:836-840.
2. Sheu KFR, Clarke DD, Kim YT, et al. Studies of transketolase abnormality in Alzheimer's disease. *Arch Neurol.* 1988;45:841-845.
3. Bowen DM, White P, Spillane JA, et al. Accelerated aging or selective neuronal loss as an important cause of dementia? *Lancet.* 1979;1:11-13.
4. Blass JP, Gleason P, Brush D, DiPonte P, Thaler H. Thiamine and Alzheimer's disease: a pilot study. *Arch Neurol.* 1988;45:833-835.
5. Folstein MF, Folstein SE, McHugh PR. A practical method for grading the cognitive state for the clinician. *J Psychiatr Res.* 1975;12:189-198.
6. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry.* 1968;114:797-811.
7. Haycox JA. A simple, reliable clinical behavioral scale for assessing demented patients. *J Clin Psychiatry.* 1984;45:23-24.
8. Zemcov A, Barclay LL, Brush D, et al. Computerized data-base for evaluation and follow-up of demented patients. *J Am Geriatr Soc.* 1984;32:801-804.
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
10. Morris JM, Heyman A, Mohs RC, et al. The consortium to establish a registry for Alzheimer's disease (CERAD), I: clinical and neuropsychological assessment of Alzheimer's disease. *Neurology.* 1989;39:1159-1165.
11. Teng EL, Chui HC, Schneider LS, Metzger LE. Alzheimer's dementia: performance on the Mini-Mental State Examination. *J Consult Clin Psychol.* 1987;55:96-100.
12. Leber P. Establishing the efficacy of drugs with psychogeriatric indications. In: Crook T, Ferris S, Bartus R, eds. *Assessment in Geriatric Psychopharmacology.* New Canaan, Conn: Powley; 1983:1-12.


Sinemet®...for many patients with Parkinson's disease, the foundation of therapy for 15 years.
Sinemet®
(Carbidopa-Levodopa)
Power and Precision
Only Sinemet® provides the power to re-establish dopamine levels in the brain and the precision to adjust dosage to meet the individual needs of the patient.



Maintaining Dopamine Levels Within the Therapeutic Window *The aim of clinical intervention in Parkinson's disease is to maintain dopamine levels within a therapeutic window. The three dosage strengths of Sinemet® help meet this challenge by providing both the power to replenish dopamine levels in the brain and the precision to adjust to individual patient needs.*

Managing Parkinson's disease therapy can be complex. The critical need is to maintain dopamine levels in the brain within an ever-narrowing therapeutic window. A window that is different in every patient and one that changes over time because of the progressive nature of the disease.

Dopamine replacement is the mainstay of therapy in Parkinson's disease. And, only Sinemet® has the power to re-establish dopamine levels in the brain.

But, power alone is not enough. Sinemet® also provides you the flexibility to meet the individual needs of the patient...by changing dosage strength or frequency...or by changing the ratio of carbidopa and levodopa.

Nothing else gives you this power and precision to manage the signs and symptoms of Parkinson's disease like Sinemet®.

As with levodopa, SINEMET* may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine levels following administration of levodopa.

Please see a brief summary of prescribing information on the adjoining page.

Sinemet®
(Carbidopa-Levodopa)

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For many patients with Parkinson's disease

Dosage Guidelines

Individualized dosage—a key to clinical success with Sinemet®

- Begin when symptoms first interfere with normal function
- Adjust as necessary to help maintain relief of symptoms

1

For initial therapy...Start with:

SINEMET 25-100

containing 25 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

one tablet t.i.d.

If necessary, to control symptoms, dosage may be increased by one tablet every day or every other day until a dosage of eight tablets of Sinemet 25-100 a day is reached.

2

When it is evident that patients need more levodopa...Transfer to:

SINEMET 25-250

containing 25 mg carbidopa (anhydrous equivalent) and 250 mg levodopa

one tablet t.i.d.

If still more levodopa is necessary, dosage with Sinemet 25-250 may be increased by one-half to one tablet every day or every other day to a maximum of eight tablets a day.

3

When individualizing dosage...Titrate with:

SINEMET 10-100

containing 10 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

or SINEMET 25-100

or SINEMET 25-250

The optimum daily dosage of Sinemet must be determined by careful titration in each patient. Tablets of the three strengths may be given separately or combined as needed to provide the optimum daily dosage.

For patients transferred from levodopa

DISCONTINUE LEVODOPA AT LEAST 8 HOURS BEFORE STARTING SINEMET. The starting dose for Sinemet should provide about 25 percent of previous levodopa requirements. (Patients receiving less than 1500 mg of levodopa a day should be started on one tablet of Sinemet 25-100 t.i.d. or q.i.d.)

Sinemet®
(Carbidopa-Levodopa)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the us of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following dru are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur whe SINEMET is added to the treatment of a patient receiving ar tihypertensive drugs. Therefore, when therapy with SINEME is started, dosage adjustment of the antihypertensive dr may be required. For patients receiving monoamine oxidas inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, i cluding hypertension and dyskinesia, resulting from the co comitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce th therapeutic effects of levodopa. In addition, the beneficial e fects of levodopa in Parkinson's disease have been reporte to be reversed by phenytoin and papaverine. Patients takin these drugs with SINEMET should be carefully observed f loss of therapeutic response.

Adverse Reactions: Most common serious adverse rea tions occurring with SINEMET are choreiform, dystonic, ar other involuntary movements. Other serious adverse rea tions are mental changes including paranoid ideation ar psychotic episodes, depression with or without developme of suicidal tendencies and dementia. Convulsions also ha occurred; however, a causal relationship with SINEMET h not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregulariti and/or palpitation, orthostatic hypotensive episode bradykinetic episodes (the "on-off" phenomenon), anore ia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulc hypertension, phlebitis, hemolytic and non-hemolyt anemia, thrombocytopenia, leukopenia, and agranulocyto have occurred.

Laboratory tests which have been reported to be abn mal are alkaline phosphatase, SGOT (AST), SGPT (ALT), la tic dehydrogenase, bilirubin, blood urea nitrogen, prote bound iodine, and Coombs test.

Other adverse reactions that have been reported w levodopa are: *Nervous System:* ataxia, numbness, increas hand tremor, muscle twitching, muscle cram blepharospasm (which may be taken as an early sign of cess dosage, consideration of dosage reduction may made at this time), trismus, activation of latent Horner's sy drome. *Psychiatric:* confusion, sleepiness, insom nightmares, hallucinations, delusions, agitation, anxie euphoria. *Gastrointestinal:* dry mouth, bitter taste, sialorrh dysphagia, bruxism, hiccups, abdominal pain and distre constipation, diarrhea, flatulence, burning sensation tongue. *Metabolic:* weight gain or loss, edema. *Integumenta* malignant melanoma (see also CONTRAINDICATION flushing, increased sweating, dark sweat, skin rash, loss of h *Genitourinary:* urinary retention, urinary incontinence, d urine, priapism. *Special Senses:* diplopia, blurred vision, dila pupils, oculogyric crises. *Miscellaneous:* weakness, faintne fatigue, headache, hoarseness, malaise, hot flashes, sense stimulation, bizarre breathing patterns, neuroleptic maligna syndrome.

Overdosage: Management of acute overdosage w SINEMET is basically the same as management of acute o dosage with levodopa; however, pyridoxine is not effect in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET 10-100, SINEMET 25-1 and SINEMET 25-250 are supplied in bottles of 100 and u dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEM 25-250 must be protected from light.

Manufactured by:
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WEST POINT, PA 19486, USA

FOR:

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Du Pont Pharmaceutical
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Brief Summary of 6219/7667300

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Sinemet®
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Nystagmus of Pelizaeus-Merzbacher Disease

A Magnetic Search-Coil Study

Jonathan D. Trobe, MD; James A. Sharpe, MD; David K. Hirsh, MD; Stephen S. Gebarski, MD

• Magnetic search-coil oculography of three brothers with clinically diagnosed Pelizaeus-Merzbacher disease disclosed the presence of binocular elliptical pendular nystagmus in two patients in whom the waveform of the nystagmus was not obvious on inspection. This study, the first reported application of high-resolution oculography to Pelizaeus-Merzbacher disease, also demonstrated primary position upbeat nystagmus in all three patients. The importance of finding this combination of elliptical pendular and upbeat nystagmus is that it is not described in any other childhood neurodegenerative states and, in combination with supportive clinical history and magnetic resonance imaging, may be so characteristic of Pelizaeus-Merzbacher disease that a strong presumptive diagnosis can be made.

(*Arch Neurol.* 1991;48:87-91)

Pelizaeus-Merzbacher disease (PMD) is an inherited disorder of central nervous system myelin, with neonatal-, childhood-, and adult-onset forms.[1] Among the leukodystrophies, PMD is distinctive in that an unusual binocular pendular nystagmus and head tremor typically herald its onset.[1]

Two previous conventional electronystagmographic studies of PMD using electro-oculographic leads showed prolonged slow phases[2] and unusually large amplitudes[3] of caloric-induced nystagmus. The authors of the latter article suggested that these electronystagmographic abnormalities might be pathognomonic of PMD.

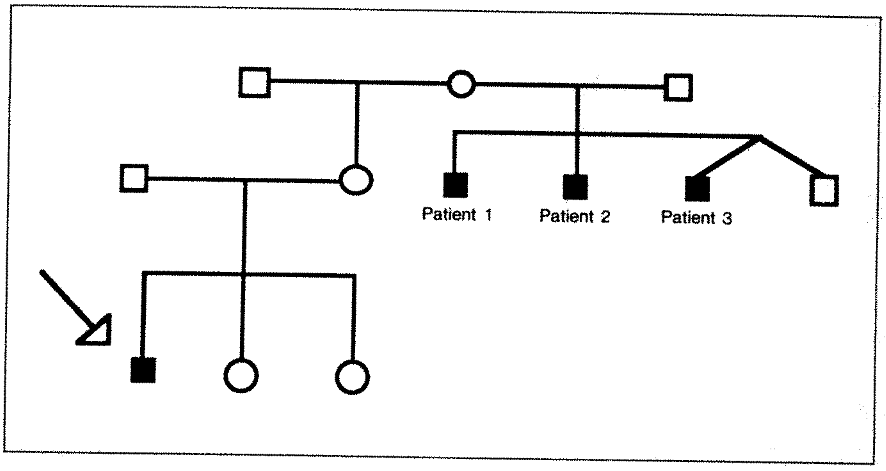
We have performed high-resolution oculographic examinations of the three maternal uncles of a 23-month-old male infant (our proband), each of whom was clinically diagnosed as having PMD (Fig 1). Our oculographic study differs from previously published reports in using a magnetic search coil, which permits more precise assessment of low-amplitude eye movements (in all directions) than does conventional electronystagmography. We did not find the previously described abnormalities of caloric-induced nystagmus,[2,3] but we documented an elliptical trajectory in two patients and a primary position upbeat nystagmus in all three patients that were not obvious by inspection.

PATIENTS AND METHODS

All three patients underwent complete neurological and neuro-ophthalmological examination, video-taping of eye movements, and magnetic resonance imaging.

Oculography was conducted on each affected adult patient, using a scleral silicone contact ring with a wire wound within its outer rim. The right eye was recorded. Patients were seated with the head centered in 0.18-cubic-meter magnetic coils consisting of two pairs of coils, one coil on each side, and one above and one below the head (CNC Engineering, Seattle, Wash). Analogue signals of eye position were direct-current coupled, amplified, low-pass filtered at 500 Hz, and recorded on analogue magnetic tape and, simultaneously, on an ink-jet rectilinear polygraph. Head position was similarly monitored with a search-coil monitor

Fig 1.—Family pedigree. Affected patients are designated by solid symbols; the proband is designated by the arrow.



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Reprint requests to W. K. Kellogg Eye Center, 1000 Wall St, Ann Arbor, MI 48105 (Dr Trobe).

Eye Movements of Three Brothers Affected With Pelizaeus-Merzbacher Disease Examined by Inspection* and Oculography†

	Patient 1		Patient 2		Patient 3	
	Inspection	Oculography	Inspection	Oculography	Inspection	Oculography
Nystagmus Primary position	None	R beat and upbeat	Vertical pendular	Elliptical pendular, R beat and upbeat	"Shimmering"	Elliptical pendular and upbeat
Right gaze	R beat	R beat	R beat	R beat	R beat	R beat
Left gaze	L beat	L beat	L beat	L beat	L beat	L beat
Upgaze	Upbeat	Upbeat	Upbeat	Elliptical pendular and upbeat	None	Elliptical pendular and upbeat
Downgaze	None	Upbeat	None	Elliptical pendular and upbeat	None	Elliptical pendular
Saccades	Normal	Hypometric to left; slow vertical	Normal	Slow downward	Normal	Slow downward
Pursuit	Saccadic	Low gain	Saccadic	Low gain	Saccadic	Low gain
Vestibulo-ocular reflex	...	Low gain	...	Normal	...	Normal
Calorics	...	Normal	...	Normal	...	Normal

*Including ophthalmoscopy.
†Magnetic search-coil oculography.

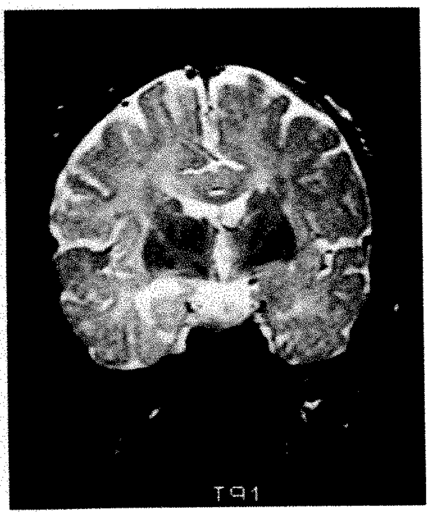

Fig 2.—Patient 1. Coronal brain magnetic resonance imaging. T_2-weighted image shows increased intensity in all visualized white matter, most notable when the gray matter intensity is compared with it. Normally, the gray matter should have higher signal than does the white matter. There is also decreased intensity in the basal ganglia, perhaps related to excessive iron deposition.

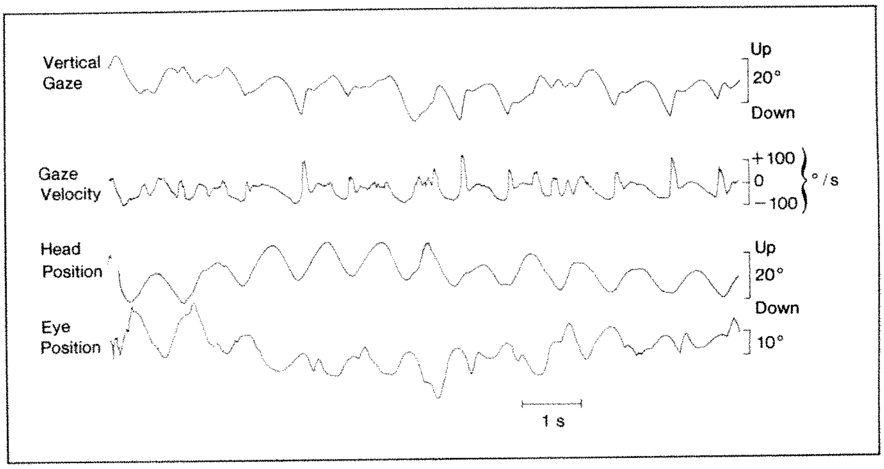

Fig 3.—Patient 1. High-resolution oculography. Vertical vestibulo-ocular reflex (VOR) during active sinusoidal motion of the head in pitch at approximately 1 Hz. The upward VOR has lower gain than does the downward VOR, so that during downward head motion, gaze (the sum of eye position plus head position) is directed downward. If the VORs were normal, vertical gaze (top channel) would be a straight line. The unbalanced VOR is compensated by upward quick phases that are evident as upward spikes of gaze velocity (second channel), causing upbeat nystagmus. Vertical saccades and nystagmus quick phases were abnormally slow.

on a lightweight headband, while the head was restrained by occipital and chin supports.

Patients viewed a rear-projected laser target reflected from mirrors mounted on galvanometer motors, subtending 0.25° of visual angle, and rear projected on a translucent screen. Eye movements were recorded while the patient fixated the target and in darkness. Pursuit movements were recorded while the patient pursued the laser target driven by a computer in sine waves, horizontally or vertically, at peak-to-peak amplitudes of 20° and frequencies of 0.25, 0.5, and 1.0 Hz. Saccades were elicited by step changes in target position at unpredictable intervals, directions, and amplitudes of 5°, 10°, and 20°.

The horizontal vestibulo-ocular reflex (VOR) was tested in darkness, while patients were seated in a vestibular chair rotated sinusoidally at peak-to-peak amplitudes of 20° and frequencies of 0.25, 0.5, and 1.0 Hz. The vertical VOR was assessed during active vertical head movement at the same peak amplitude and frequencies, while head movement was paced with the sound of a metronome. Patients attempted to fixate an imaginary stationary target in darkness.

REPORT OF CASES (Table)

CASE 1.—This 25-year-old man developed abnormal eye movements at 6 weeks of age. He was diagnosed as having had cerebral palsy at the age of 18 months because of delayed milestone acquisition. At the age of 5 years, he had been described as having had esotropia, bilateral nystagmus, and pale optic discs. By the age of 12 years, he was wheelchair bound. On our examination, at the age of 25 years, he was alert and oriented in all spheres, knew the president's name, and could do simple addition and spelling. His speech was scanning. Upper extremity strength was normal, but lower extremity strength was 1/5 with marked spasticity, and all limbs displayed ataxia. Muscle stretch reflexes were hyperactive, with clonus at the ankles, and plantar reflexes were extensor bilaterally. Sensation was normal.

His visual acuity was 20/80 OD, and 20/100 OS. There was temporal optic disc pallor bilaterally. His eyes were aligned in all positions of gaze. Nystagmus was not evident in the primary position, but the patient had horizontal jerk nystagmus in the extremes of lateral gaze and upbeating nystagmus in upgaze. Saccadic velocities were normal, and pursuit movements were saccadic.

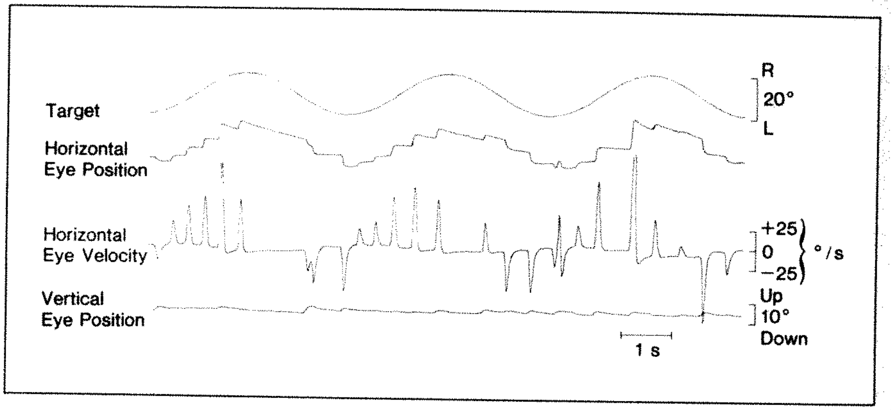

Fig 4.—Patient 1. High-resolution oculography. Horizontal smooth pursuit of a 0.25-Hz target is saccadic to the right. The horizontal eye calibration (channel 2) is the same as the target calibration (channel 1). The fourth channel illustrates low-amplitude upbeat nystagmus in the primary position; upward quick phases are slowed, as are all vertical saccades. R indicates right; and L, left.

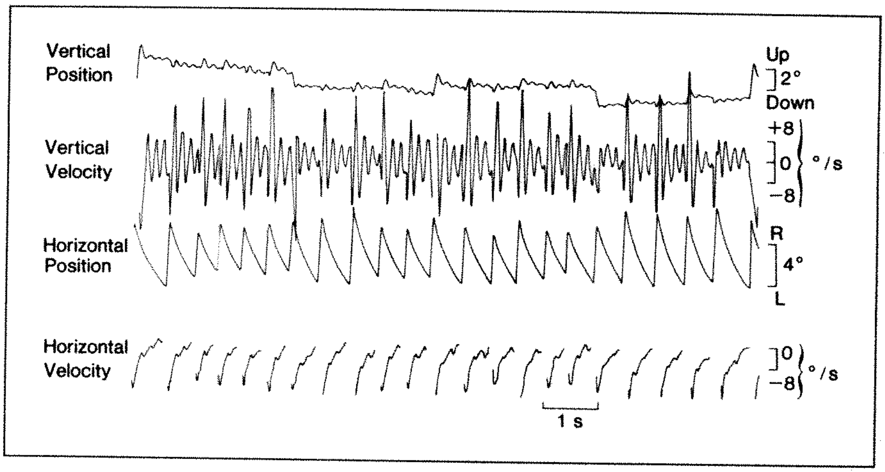

Fig 5.—Patient 2. High-resolution oculography reveals low-amplitude vertical pendular nystagmus superimposed on upbeat nystagmus. The eye is near the vertical midposition. The horizontal position demonstrates right-beating nystagmus, and the horizontal velocity record (bottom trace) shows sinusoidal oscillations superimposed on the leftward slow phases of the horizontal nystagmus. Since the large (0.2° to 0.3°) amplitude vertical pendular oscillations are 90° out of phase, with the miniature horizontal oscillations, the pendular nystagmus is elliptical. The combination of upbeating and right-beating nystagmus also caused diagonal jerk nystagmus. R indicates right; and L, left.

Magnetic resonance imaging (T_2-weighted) demonstrated very severe brain atrophy, increased signal in white matter, and decreased signal in basal ganglia and thalami (Fig 2), a pattern considered typical of PMD.[4-7]

The oculographic examination revealed primary position rightward-beating nystagmus that increased on rightward gaze, and leftward-beating nystagmus on leftward gaze. There was upbeating nystagmus in primary position, upgaze, and downgaze that did not change in the darkness (Fig 3). Horizontal saccades had normal velocity and latency, but they were hypometric to the left and accurate to the right. Upward saccades were mildly slowed, and downward saccades had very reduced peak velocities. Both horizontal (Fig 4) and vertical smooth pursuits were severely reduced in velocity. The upward VOR had very low gain (ratio of smooth eye movement velocity to head velocity), and the downward VOR had mild gain reduction. Warm- (44°C) and cold- (30°C) water caloric responses from each ear were normal.

Case 2.—This 22-year-old man was also diagnosed as having cerebral palsy. His mother noticed his nystagmus before he was 2 months old. At the age of 4 years, he was found to have vertical pendular nystagmus and normal optic discs. He never reached normal cognitive development and became wheelchair bound at 15 years of age. On our examination, at 22 years of age, he was fully oriented. His speech was fluent, although scanning. Both short- and long-term memory were good, yet he was poor at calculations and unable to interpret proverbs. His muscle strength and bulk were normal in the arms, although finger dexterity was poor. Lower extremity strength was 5/5 proximally with increased tone and 1/5 distally with decreased tone and bulk. He had severe truncal and appendicular ataxia. Muscle stretch reflexes were 1+ in the arms and 3+ at the knees, with sustained clonus at the ankles. Plantar responses were flexor. Sensation was intact.

His visual acuity was 20/70 OD and 20/80 OS. Pupillary reactions, color vision, and confrontation visual fields were normal. There was bilateral optic disc pallor. He had a 40-prism-diopter esotropia in primary position. The eyes appeared to be still in the primary position, but ophthalmoscopic examination showed pendular nystagmus. There was horizontal jerk nystagmus on right and left lateral gaze, and upbeat nystagmus on upgaze. Saccadic velocities were grossly normal, and pursuit movements were saccadic.

Magnetic resonance imaging revealed severe cerebral cortical, midbrain, and cerebellar atrophy. The T_2-weighted images demonstrated diffusely increased white matter signal, most notable in the cerebrum. The signal aberrations were similar but less marked than those in patient 1.

The oculographic examination revealed vertical and horizontal pendular nystagmus in the primary position, with the vectors approximately 90° out of phase, causing an elliptical trajectory. The pendular nystagmus persisted in darkness. A low-amplitude (1°) upbeat nystagmus was superimposed on the pendular nystagmus (Fig 5); it increased in amplitude on upgaze. The vertical amplitude of pendular nystagmus was 12 to 20 arc-minutes peak to peak, and the horizontal amplitude was 3 to 4 arc-minutes peak to peak. There was rightward-beating nystagmus in primary position and on rightward gaze, and leftward-beating nystagmus on leftward gaze. Upward saccadic velocities were normal, but downward velocities were slow. Vertical and horizontal pursuit movements had low gain (ratio of smooth eye movement velocity to target velocity). Vertical and horizontal VOR gains were normal. Warm- and cold-water caloric stimulations of each ear showed normal slow phases of nystagmus.

Case 3.—This 20-year-old man was noted to have nystagmus at about 2 months of age. He was slow to acquire developmental milestones and, like his brothers, was diagnosed as having had cerebral palsy. At 3 years of age, he was described as having had a 10-prism-diopter intermittent esotropia, coarse pendular nystagmus in all fields of gaze, and slightly pale optic discs. At 20 years of age, he ambulated with Canadian crutches. His speech was dysarthric. Strength was nearly full in the arms and legs, but only 3/5 in the feet. Muscle tone was normal in the arms and increased in the legs. He had moderate ataxia. Muscle stretch reflexes were 3+ at the elbows and 1+ elsewhere, with clonus at the ankles. Extensor plantar responses were present bilaterally.

The patient's visual acuity was 20/200 OD and 20/200 OS. There was bilateral optic disc pallor. Saccadic velocities were normal, and smooth pursuit was saccadic. He had fine shimmering eye movements in the primary position, with a larger vertical than horizontal component. On right and left lateral gaze, there was large-amplitude low-frequency laterally beating jerk nystagmus.

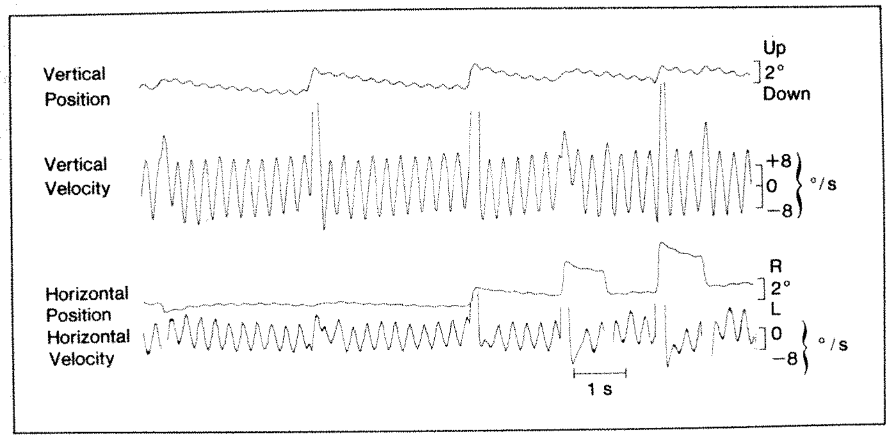

Fig 6.—Patient 3. High-resolution oculography. Pendular nystagmus is evident in the vertical and horizontal positions and velocity records. The amplitude of the vertical oscillations was about twice that of the horizontal oscillations. The vertical and horizontal oscillations are 20° out of phase, so that the elliptical nystagmus resulting from the amplitude and phase disparity between the vertical and horizontal oscillations is almost diagonal. The eyes move up to the left and down to the right. Upbeat nystagmus is evident in the vertical position trace. The vertical pendular nystagmus is superimposed on the slow phases of the upbeat nystagmus. The patient was attempting to fixate a stationary target. Both the elliptical and the upbeat nystagmus persisted unchanged in darkness. R indicates right; and L, left.

Magnetic resonance imaging showed moderate brain atrophy, and T_2-weighted images demonstrated white-matter signal aberrations similar to those of patient 2, but less prominent.

The oculographic examination revealed elliptical pendular nystagmus in the primary position, with the horizontal and vertical vectors approximately 20° out of phase. The vertical pendular oscillations had a peak-to-peak amplitude of 30 to 45 arc-minutes, and the horizontal pendular oscillations had peak-to-peak amplitudes of 8 to 12 arc-minutes (Fig 6), a waveform that was not altered by darkness. Primary position upbeat nystagmus was superimposed on the elliptical nystagmus. Horizontal and upward saccades were of normal velocity; downward saccades were slowed. Vertical and horizontal smooth pursuit velocities were mildly reduced in all directions. The vertical and horizontal VOR gains were normal. Warm-water caloric responses were normal in each ear.

This patient has a fraternal twin brother who refused physical examination. His family described him as physically normal, being able to hold a manual job and drive a car, but learning disabled such that he could not finish high school.

Our proband, aged 23 months, could not be studied oculographically because of his age. To external inspection and on ophthalmoscopy, he displayed an elliptical pendular nystagmus in all positions of gaze. White blood cell arylsulfatase A and galactocerebrosidase activities and plasma levels of very-long-chain fatty acids were normal.

COMMENT

Seitelberger[1] divided the clinical patterns of PMD by age at onset into six types, the most common of which are classical (infantile-onset), connatal (present at birth), and the Lowenberg-Hill (adult-onset) type. The classical and connatal forms of PMD typically have X-linked recessive inheritance, whereas the adult-onset type has autosomal dominant inheritance.[1] However, there are cases of both classical[8] and connatal[9] PMD with apparent autosomal recessive inheritance.

Of the infantile form, Pelizaeus[10] wrote "... the disorder manifested itself during infancy by aimless, wandering eye movements," referring to the nystagmus, which, together with head tremor, make up the first signs of PMD. Often described as "wobbly" or pendular, the nystagmus is followed by progressive spasticity, ataxia, tremor, choreiform or athetotic movements, optic atrophy, and cognitive deterioration. Death usually occurs within the first few years of life in the connatal form of PMD and in the second or third decade of life in the classical form.

Koeppen et al[11] found the absence of a myelin protein, called *proteolipid apoprotein* (proteolipid protein PLP or lipophilin), in two cases of PMD from a family with X-linked recessive inheritance. The authors suggested that the absence of proteolipid protein results in defective assembly of myelin sheaths, thus making PMD a dysmyelinating disease.

Nystagmus is a critical distinguishing feature of PMD, whose differential diagnosis includes metachromatic leukodystrophy, adrenoleukodystrophy, Krabbe disease, Cockayne's syndrome, and neuroaxonal degeneration.[12] To our knowledge, none of these entities is associated with the pendular nystagmus found in PMD, except Cockayne's syndrome,[13] an autosomal recessive leukodystrophy with a pattern of myelin loss histologically similar to PMD. Indeed, Seitelberger[1] considered Cockayne's syndrome to be a special type of PMD. It is distinguished from PMD by multiple dysmorphic features and the presence of basal ganglia calcifications.[13,14]

If other neurologic signs of PMD, besides nystagmus, are not yet prominent, then a sporadic case of PMD may be confused with congenital nystagmus or spasmus nutans. Congenital nystagmus is a binocular pendular or jerk nystagmus, which is almost always horizontal, rarely purely vertical, and may be associated with head tremor.[15,16] Most infants with congenital nystagmus are otherwise neurologically normal.[17] In its complete form, spasmus nutans is a syndrome consisting of a triad of pendular (usually horizontal) nystagmus, head nodding, and torticollis, with onset in the first year of life. It is infrequently associated with central nervous system pathology, and usually resolves spontaneously in 1 to 4 years.[17,18]

Magnetic search-coil oculography in our patients with PMD disclosed, in two of the three patients, a pattern of pendular nystagmus that has not been reported to appear in any other childhood neurodegenerative disorders. Its distinctive waveform, which could not be resolved by inspection, consisted oculographically of a sinusoidal oscillation in both eyes, with horizontal and vertical vectors that were out of phase, and of unequal amplitude, making the eyes' trajectory elliptical. We could not confirm the previously reported conventional electronystagmographic findings of prolonged slow phases and unusually large amplitudes of caloric-induced nystagmus.[2,3]

Pendular nystagmus is acquired in two diseases affecting adults: multiple sclerosis[19] and brain-stem stroke.[20] In some cases, this pendular nystagmus is associated with synchronous oscillations of the palate and other branchial muscles, a combination termed *oculopalatal myoclonus*.[21] In a study of 35 cases of acquired pendular nystagmus in multiple sclerosis, Aschoff et al[19] concluded that it resulted from cerebellar nuclear damage. Gresty et al[22] suggested instead that the responsible lesion is located near the oculomotor nuclei.

A feature common to each of our patients was upbeat nystagmus in primary position. Previous clinical pathological correlations of upbeat nystagmus have identified damage in the pontomedullary tegmentum.[23-26] This may be explained by disruption of the ventral tegmental pathway for the upward VOR, causing imbalance in the vertical VOR.[27] Thus, there is evidence to implicate dysmyelination in the pontomedullary tegmentum as the probable cause of the upbeat nystagmus and, perhaps, the elliptical nystagmus as well. Normality of the horizontal and vertical VORs in our patients implies that involvement of vestibular smooth eye movement pathways is not responsible for the elliptical pendular nystagmus of PMD.

We suggest that the value of recording eye motion in PMD by a high-resolution technique such as search coil lies in verifying the elliptical pendular and upbeat nystagmus that often cannot be resolved by inspection. The presence of this distinctive eye movement abnormality, in conjunction with appropriate magnetic resonance imaging findings, strongly supports a diagnosis of PMD.

This study was supported by Medical Research Council of Canada grants ME5509 and MT5404 (Dr Sharpe).

References

1. Seitelberger F. Pelizaeus-Merzbacher disease. In: Vinken PJ, Bruyn GW. *Handbook of Clinical Neurology*. Amsterdam, the Netherlands: North Holland: 1970;10:150-202.
2. Lott IT, Parker SW, Herndon RM, Moser HW. Demyelination in Pelizaeus-Merzbacher disease. *Pediatr Res.* 1981;15:1590.
3. Mallinson AI, Longridge NS, Dunn HG, McCormick AQ. Vestibular studies in Pelizaeus-Merzbacher disease. *J Otolaryngol.* 1983;12:361-364.
4. Penner MW, Li KC, Gebarski SS, Allen RJ. MR imaging of Pelizaeus-Merzbacher disease. *J Comput Assist Tomogr.* 1987;11:591-593.
5. Journel H, Roussey M, Gandon Y, Allaire C, Carsin M, le Marec B. Magnetic resonance imaging in Pelizaeus-Merzbacher disease. *Neuroradiology.* 1987;29:403-405.
6. Shimomura C, Matusi A, Choh H, Funahashi M, Suzuki Y, Tsuchiya K. Magnetic resonance imaging in Pelizaeus-Merzbacher disease. *Pediatr Neurol.* 1988;4:124-125.
7. Shiomi M, Ookuni H, Sugita T. Auditory brainstem response, CT and MR imaging in a family with Pelizaeus-Merzbacher disease. *No To Hattatsu.* 1987;19:210-215.
8. Pamphlett R, Silberstein P. Pelizaeus-Merzbacher disease in a brother and sister. *Acta Neuropathol (Berl).* 1986;69:343-346.
9. Cassidy SB, Sheehan NC, Farrell DF, Grunnet M, Holmes GL, Zimmerman AW. Connatal Pelizaeus-Merzbacher disease: an autosomal recessive form. *Pediatr Neurol.* 1987;3:300-305.
10. Pelizaeus F. Über eine eigentumliche Form spastischer Lahmung mit cerebräler-scheinungen auf hereditärer Grundlage (multiple Sklerose). *Arch Psychiatr Nervenkr.* 1885;16:698.
11. Koeppen AH, Ronca NA, Greenfield EA, Hans MB. Defective biosynthesis of proteolipid protein in Pelizaeus-Merzbacher disease. *Ann Neurol.* 1987;21:159-170.
12. Johnson WG. Lysosomal diseases and other storage diseases. In: Rowland LP, ed. *Merritt's Textbook of Neurology*, 7th ed. Philadelphia, Pa: Lea & Febiger; 1984:391-418.
13. Coker S, Susac JO, Sharpe JA, Smallridge B. Cockayne's syndrome: neuro-ophthalmic, CAT scan and endocrine observations. In: Smith JL. *Neuro-Ophthalmology Focus 1980.* New York, NY: Masson Publishing USA Inc; 1979:379-385.
14. Dabbagh O, Swaiman KF. Cockayne syndrome: MRI correlates of hypomyelination. *Pediatr Neurol.* 1988;4:113-116.
15. Gresty M, Page N, Barratt H. The differential diagnosis of congenital nystagmus. *J Neurol Neurosurg Psychiatry.* 1984;47:936-942.
16. Dell'Osso LF, Daroff RB. Congenital nystagmus waveforms and foveation strategies. *Doc Ophthalmol.* 1975;39:155-182.
17. Jacobson DM, Corbett JJ. Nystagmus. *Semin Ophthalmol.* 1987;2:183-208.
18. King RA, Nelson LB, Wagner RS. Spasmus nutans: a benign clinical entity? *Arch Ophthalmol.* 1986;104:1501-1504.
19. Aschoff JC, Conrad B, Kornhuber HH. Acquired pendular nystagmus with oscillopsia in multiple sclerosis: a sign of cerebellar disease. *J Neurol Neurosurg Psychiatry.* 1974;37:570-577.
20. Lawrence WH, Lightfoote WE. Continuous vertical pendular eye movements after brainstem hemorrhage. *Neurology.* 1975;25:896-898.
21. Guillain G. The syndrome of synchronous rhythmic palato-pharyngo-laryngo-oculo-diaphragmatic myoclonus. *Proc R Soc Med.* 1938;31:1031-1038.
22. Gresty MA, Ell JJ, Findley LJ. Acquired pendular nystagmus: its characteristics, localizing value and pathophysiology. *J Neurol Neurosurg Psychiatry.* 1982;45:431-439.
23. Lapresle J, Hamida B. The dentato-olivary pathway: somatotopic relationship between the dentate nucleus and the contralateral inferior olive. *Arch Neurol.* 1970;22:135-143.
24. Keane JR, Itabashi HH. Upbeat nystagmus: clinicopathologic study of two patients. *Neurology.* 1987;37:491-494.
25. Fisher A, Gresty M, Chambers B, Rudge P. Primary position upbeat nystagmus: a variety of central positional nystagmus. *Brain.* 1983;106:949-964.
26. Gilman N, Baloh RW, Tomiyasu U. Primary position nystagmus. *Neurology.* 1977;27:294-298.
27. Ranalli PJ, Sharpe JA. Upbeat nystagmus and the ventral tegmental pathway of the upward vestibulo-ocular reflex. *Neurology.* 1988;38:1329-1330.

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Please see following page for brief summary of prescribing information.

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Cafergot® (ergotamine tartrate and caffeine) Tablet

ergotamine tartrate USP	1 mg
caffeine USP	100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

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ergotamine tartrate USP	2 mg
caffeine USP	100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

Cafergot® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

ACTIONS: Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS

Cafergot® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

PRECAUTIONS: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

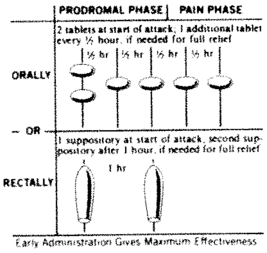
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief
½ hr
½ hr
½ hr
½ hr
ORALLY
— OR —
1 suppository at start of attack, second suppository after 1 hour, if needed for full relief
1 hr
RECTALLY

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE: The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

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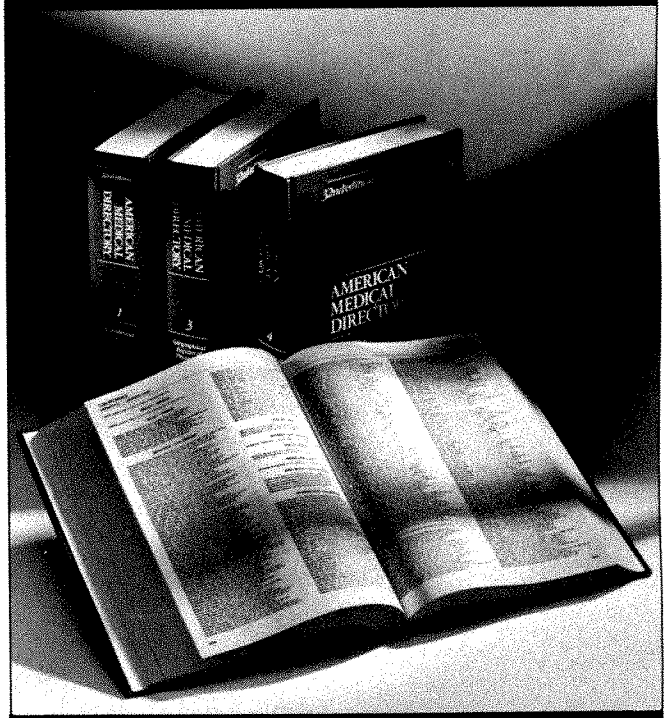

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History of Neurology

James Parkinson

On Child Abuse and Other Things

Robert D. Currier, MD, Mary M. Currier, MD, MPH

• James Parkinson, a general physician, was interested in all facets of medical care, and wrote two books for the lay public that contained comments on diverse things. He may have been one of the first physicians to publicly describe child abuse. Some of his advice to the public was of a neurologic nature, and included directions on the diagnosis and treatment of pseudoseizures, epilepsy, drowning, and stroke.

(*Arch Neurol.* 1991;48:95-97)

In his pamphlet, *The Villager's Friend and Physician*, James Parkinson wrote with emotion on child abuse after an encounter in his practice.

> The disease which I shall next speak of is often in its first stage mistaken for the effect of worms. DROPSY OF THE BRAIN, or WATERY HEAD, may be suspected when a child appears uncommonly heavy and dull, complains of pain in the head, has its sleep disturbed with alarming dreams, reluctantly moves its head from the pillow, or attends to surrounding objects; and is affected with frequent sickness and slight fever. . . .[1(p62)]
>
> This complaint is frequently occasioned by the falls on the head which children are exposed to on first going alone. Guard their heads, therefore, at this time, with the old fashioned headdress for children, a quilted stuffed cap, or pudding. I am sorry to be obliged to add another cause of this malady, severe blows on the head, inflicted in the correction of children. Parents too often forget the weight of their hands and the delicate structure of a child. You must excuse the digression—it was but yesterday I passed the cottage of one you all know to have always neglected his children; I heard the plaintive and suppliant cries of a child, and rushed into the cottage; where I saw the father, whose countenance was dreadful, from the strong marks of passion and cruelty which it bore, beating most unmercifully his son, about ten years old. The poor countenance would, one would have supposed, obtained mercy from the most obdurate; it was shrunk up with dread and terror; the most earnest and humble supplications proceeded from his lips, whilst his eyes were fixed with horror on the impending instrument of his chastisement. I stopped the brute from proceeding in his violent outrage, asking what was the crime the boy had committed, and found he had not finished the task of work he had set him. 'Ah, John', I exclaimed, 'consider how you ever neglected your children; you have never troubled yourself to give them good advice nor refrained from setting them bad examples. The crimes of the children of such a parent must be on his head: you merit correction and not he, for you never showed him what it was to be industrious. Expect not duty from a child, if you have not done yours toward him. Duties are required of parents as well as of children; and though an undutiful child may be termed a monster, know that the worst of monsters is an *undutiful parent*.' The wretch growled at the interruption he had suffered; and I need hardly say, manifested no compunction or regret, at his cruelty.[1(p63)]

This must be one of the earliest published comments by a physician on child abuse. Philosophers and writers had proclaimed on it back to biblical times, but did any physician write on it prior to James Parkinson in the year 1800?[2]

In this pamphlet, entitled *The Villagers Friend and Physician; or a Familiar Address on the Preservation of Health, and the Removal of Disease, on Its First Appearance; Supposed to be Delivered by a Village Apothecary. With Cursory Observations on the Treatment of Children, on Sobriety, Industry, etc. Intended for the Promotion of Domestic Happiness* (Fig 1), Parkinson also vented his opposition to wet nursing.

> . . . one more word respecting your children and I have done. Consider it as your first duty to see that your child is not robbed of that food which nature has provided for it in the breast of its mother. Should the mother be tempted for a sordid bribe to transfer to another her child's inestimable right, let her consider, that when she sells the food of her child, she perhaps also sells its life.[1(p83)]

And he concluded the small volume,

> Your next duty is the promotion of your child's happiness. As health is necessary to happiness your watchfulness over him in this respect is indispensable; since by delay, neglect, or ill placed confidence, disease may be so fixed in him as to render him miserable all the rest of his days and even to rob you of him at once. Not less necessary to his happiness is the regulation of even his infant passions and the teaching him to distinguish accurately between right and wrong.
>
> Consider the sacred trust which thus devolves to you, and carefully fulfill this delightful duty. Permit not an unbounded indulgence, lest your child acquire such a disposition, as may be a fruitful source of wretchedness to him and you, and render him odious to all around him. But, on the other hand, exercise the importance privilege of correction with mercy. Contemplate the countenance of the poor child who suffers frequent and severe chastisement; observe every feature contracted by habitual

---

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From the Department of Neurology, University of Mississippi Medical Center (Dr R. D. Currier) and the Mississippi State Department of Health (Dr M. M. Currier), Jackson.

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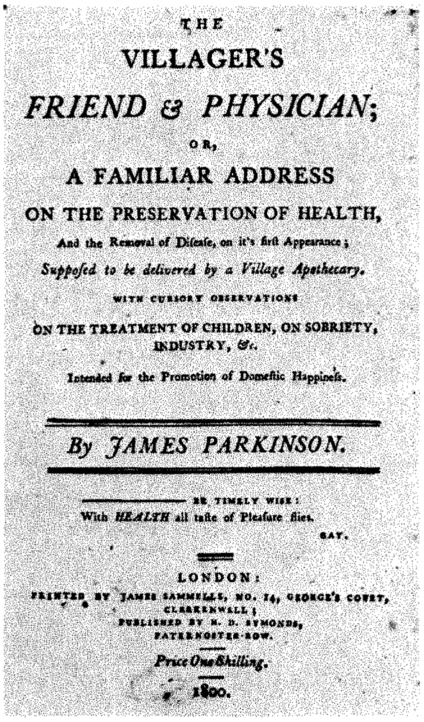

THE
VILLAGER'S
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OR,
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And the Removal of Diſeaſe, on it's firſt Appearance;
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By JAMES PARKINSON.

——— BE TIMELY WISE:
With *HEALTH* all taſte of Pleaſure flies.
GAY.

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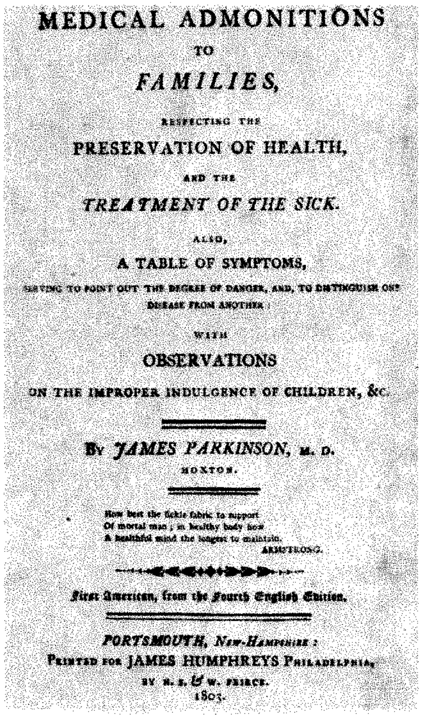
Price One Shilling.
1800.

Fig. 1.—Title page of *The Villager's Friend.*



MEDICAL ADMONITIONS
TO
FAMILIES,
RESPECTING THE
PRESERVATION OF HEALTH,
AND THE
TREATMENT OF THE SICK.
ALSO,
A TABLE OF SYMPTOMS,
SERVING TO POINT OUT THE DEGREE OF DANGER, AND, TO DISTINGUISH ONE
DISEASE FROM ANOTHER:
WITH
OBSERVATIONS
ON THE IMPROPER INDULGENCE OF CHILDREN, &C.

BY *JAMES PARKINSON*, M. D.
HOXTON.

How best the fickle fabric to support
Of mortal man; in healthy body how
A healthful mind the longest to maintain.
ARMSTRONG.

First American, from the Fourth English Edition.

PORTSMOUTH, New-Hampshire:
Printed for JAMES HUMPHREYS Philadelphia,
by N. S. & W. Peirce.
1803.

Fig. 2.—Title page of *Medical Admonitions.*

> terror. The most innocent action is performed with alarm and dread. He hardly recovers the shock the system has sustained by one series of suffering, before a fresh series begins. When this is the case, rely upon it the life of that child is iniquitously shortened and the parent is guilty of murdering his child by almost incessant torments.[1(p84)]

Much of Parkinson's general practice must have been pediatrics. He was not above trying original or unusual treatment. In discussing epilepsy in his larger book *Medical Admonitions to Families Respecting the Health and Treatment of the Sick* (1st American edition published 1803) (Fig 2), he also directed the public in health care and mentions the violent gusts of passion that would seize a 7-year-old girl terminating in an epileptic fit. Relief under other physicians was unsuccessful, and finally a friend recommended a remedy that, if done strictly, would always produce a cure. Parkinson gave the prescription as follows:

> Take two ounces of blood about the time of the moon becoming full from the arm of the patient and stir into it a tea spoonful of salt. This mixture must be swallowed while still warm. If the patient experiences any return of the fits the bleeding must be repeated and the blood again drunk on the ninth morning mixed with the salt as before.

Parkinson commented on the success of this remedy.

> The blood was taken away and the horrid potion drank but neither the one nor the other was accomplished without exciting in the unfortunate subject of the experiment the strongest signs of repugnance and horror. Indeed the experiment would not have been made so great a degree of aversion was manifested by the patient had not the parents placed great reliance on a remedy which besides being so strongly recommended was by its uncommoness and by the attention required to be paid to the state of the moon and to certain days well calculated to inspire an extraordinary degree of expectation. Complete success was the reward of their resolution for not only was the return of the fit prevented but a most unexpected event took place, the child was no longer prone to those violent gusts of passion to which she had hitherto been subject.

And he concluded,

> The child could not avoid making the conclusions that to avoid this terrific and disgusting process it was absolutely necessary that she should repress her passionate exertions and that it was much better to submit to the will of her parents than to be again forced to swallow her own blood.[3(p484)]

Parkinson gave very modern sounding instructions about what to do for epilepsy or falling sickness. He recommended that the patient should be protected from injuring himself and therefore should be placed on a bed. The clothing should be loosened and the head moderately elevated. Some substance should be introduced and held between the teeth to prevent their closing on the tongue, but this should not be anything fragile such as earthenware or glass,

> Less from the delirious state which occurs in the interval of the convulsion or from the convulsion itself suddenly coming on he should bite out a piece of the edge of the cup or glass and thereby get the sharpened broken fragments within his mouth.[3(p385)]

In the same volume, Parkinson repeated the directions given by the Royal Humane Society about resuscitation of the drowned. The recommendations were as follows:

> 1. Convey carefully the body with head raised to the nearest receiving house.
> 2. Strip, dry the body, clean the mouth and nostrils.
> 3. Young children to be put between two persons in a warm bed.
> 4. An adult—Lay the body on a bed and in cold weather near the fire.
> 5. The body to be *gently rubbed* with flannel sprinkled with spirits or flower of mustard. The proper substances to be sprinkled on flannels and a heated warming pan, covered, may be lightly moved over the back and spine—Salt never to be employed.
> 6. The breath to be fomented with hot spirits. Hot bricks or tiles, covered, etc. to be applied to the soles of the feet and palms of the hands. If no signs of life appear the body could be put into the warm bath.
> 7. To restore breathing—introduce the pipe of a bellow (when no apparatus is at hand) into one nostril, the other, and the mouth, being closed, *inflate the lungs* until the breast be a little raised; the mouth and nostrils must then be let free. Repeat this process til life appears.
> 8. Tobacco smoke is to be gently thrown into the fundament, with a proper instrument, or the bowl of a pipe covered so as to defend the mouth of the assistant.
> 9. Electricity to be early employed either by the medical assistants, or other judicious practitioners.[3(p377)]

After more instructions for various other causes of unconsciousness the conclusion was that "the plans of resuscitation are to be used for three or four hours" and "it is an absurd and vulgar opinion to suppose persons irrecoverable because life does not soon make its appearance." And finally, "bleeding never to be employed unless by the direction of the medical assistants."[3(p380)]

So, in Parkinson's time, public recommendations included the employment of artificial means to restore breathing, a recommendation that was later to be forgotten and only in the past few decades rediscovered.

Who was James Parkinson? He was a practicing physician at One Hoxton Square in Shoreditch in northeast London, as was his father before and his son after him. A busy man with a wife and five children he was involved in church work and strongly interested in politics, especially liberal causes and, in fact, dangerously involved in politics in the first half of his life. He wrote political pamphlets under the pseudonym Old Hubert and was accused of playing a part in the popgun plot against George III. Clear thinking and logical, he disliked dishonesty and the incorrectness of things as they were then and tried to stimulate reforms. He also was the author of one of the first comprehensive textbooks on fossils in the English language, wrote a pocket textbook on chemistry and one on gout, and was not above suggesting that medical education reforms were in order in another book. It would have been hard to know which area interested him the most at any one phase in his life.

Certainly he was gifted with the pen. McMenemey,[4] who wrote a comprehensive biography, comments that his sentences were long and involved and yet could be clearly understood, either the result of a unique gift or careful thought in writing, or both. The two books quoted here were designed for the lay public and must have been among the first such books in English.

Of course his *Essay on the Shaking Palsy* is one of the finest descriptions of disease of all time, but he also commented on other neurological events. In the same two volumes he distinguished between apoplexy and palsy. Apoplexy:

> In this disease, the whole of the senses, and of the voluntary motions, are in some degree abolished whilst the actions of the heart and lungs continue. The appearance of the patient is that of one in a deep sleep; the breathing being mostly accompanied by a loud snoring.[3(p352)]

He did not recognize that he was describing intracerebral hemorrhage, but did recommend bleeding for apoplexy and not for palsy. Palsy could occur in those who had had apoplexy

> Such persons as have been already described, in the preceding chapter, as predisposed to attacks or apoplexy, are also very liable to paralytic affections.[3(p366)]

Furthermore, he recognized that sometimes symptoms occurred before the apoplectic attack.

> Sometimes this disease comes on suddenly; but most frequently it is preceded by these symptoms. The face for sometime before appears more than usually florid and the eyes slightly bloodshot. The head is giddy and frequently affected with pain, particularly in the back of it. The extremities also are frequently affected with numbness, and irregularities, or inability of motion; and sometimes a little faltering of speech may be discoverable. The patient is almost constantly drowsy, and generally sleeps particularly sound; but is sometimes affected with fits of the *incubus* or nightmare. A troublesome ringing noise is frequently perceived in the ears; transient irregularities both in sight and hearing are frequently discovered, and every sense appears at times to be somewhat impaired. Recollection, reflection and every other process of the mind, is performed evidently with lessened power.[3(p353)]

Was Parkinson also the first person to describe transient ischemic attacks? He commented on risk factors:

> The subjects of the disease are generally persons in an advanced stage of life. Those who have been observed to be particularly disposed to it, who are of a corpulent habit, and have a large head and short neck. Indolence, and indulgence in the luxuries of the table, as well as the suppression of any discharge which by its length of continuance has been suffered to have become habitual to the constitution, contribute much to the forming of a predisposition of this disease.[3(p353)]

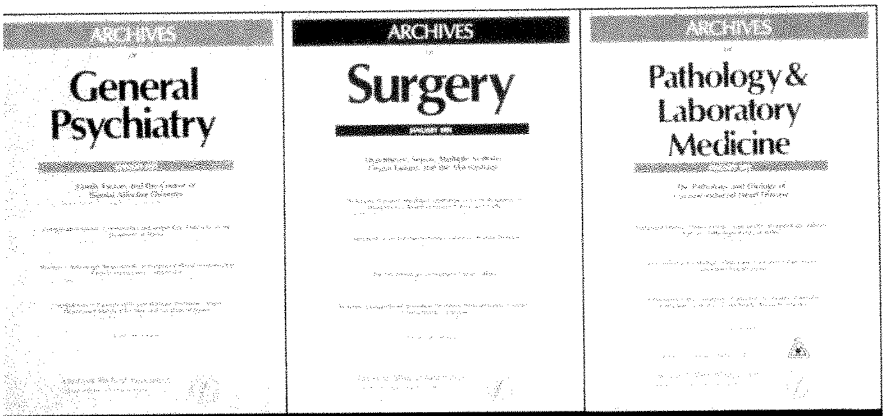
He later said that anything that interrupts the return of blood from the head may prove an exciting cause of apoplexy, as may violent exertion, especially if accompanied by full and long continued inspiration, a considerable degree of fatigue, excessive heat or cold, violent coughing, long-continued stooping posture or with the neck in an oblique position, anything worn tight about the neck, intoxication, distention of the bowels, and violent emotions. Under palsy he mentioned in addition that extreme coldness and dampness of the atmosphere play a part since the attacks are more frequent at the first setting in of winter, occur in those who lead sedentary lives and are engaged in night studies, those who suffer much distress and anxiety, and the immoderate use of spiritous liquors, tobacco, coffee, and tea will be likely to promote the production of the complaint.[3(p366)]

Parkinson even recommended certain therapies. "Exercise should be regularly employed." But electricity is not advisable, it might actually make the palsy worse.

The list of those who have written on Parkinson starts with Rowntree's tribute in 1912, in which he very carefully summarized the prior writings.[5] The most extensive biographies are those of McMenemey in 1955[4] and the recent book by Morris in 1989,[6] for which we can thank Clifford Rose who saved the manuscript from oblivion after Dr Morris' death. Comments by others, including Williamson,[7] Eyles,[8] McHenry,[9] Schulte,[10] and Jefferson,[11] have been added over the years, and Yahr,[12] Richard and Kenneth Tyler,[13] Pearce,[14] and Herzberg[15] have more recently kept the torch alight for the man. We thought it worthwhile to recall from these two relatively unknown books some of his two-century-old recommendations in pediatrics, general practice, and neurology that have not heretofore been publicly acknowledged, and to suggest he may have been the first physician to comment on child abuse.

References

1. Parkinson J. *The Villager's Friend & Physician;* or, *A Familiar Address on the Preservation of Health.* London, England: H. D. Symonds; 1800: 62, 63, 83, 84.
2. Robin, M. Historical introduction. In: Newberger EH, ed. *Sheltering Arms: The Roots of Child Protection in Child Abuse.* Boston, Mass Little Brown & Co: 1982.
3. Parkinson J. *Medical Admonitions to Families, Respecting the Preservation of Health and the Treatment of the Sick.* Philadelphia, Pa: James Humphreys; 1803: 352, 353, 366, 377, 380, 385, 484.
4. McMenemey WH. James Parkinson, 1755-1824, A Biographical Essay. In: Critchley M, ed. *James Parkinson (1755-1824).* New York, NY: Macmillan & Co Ltd; 1955.
5. Rowntree LG. James Parkinson, MD. *Bull Johns Hopkins Hosp.* 1912;23:33-45.
6. Morris AD. *James Parkinson, His Life and Times.* Boston, Mass: Birkhauser; 1989 History of Neuroscience series vol 2.
7. Williamson RT. James Parkinson and his essay on paralysis agitans. *Janus.* 1925;29:193-197.
8. Eyles JM. James Parkinson (1755-1824). *Nature.* 1955;176:580-581.
9. McHenry LC. Surgeon and paleontologist, James Parkinson. *J Oklahoma State Med Assoc.* 1958;51:521-523.
10. Schulte BPM. James Parkinson, neuroloog, paleontoloog en pamfletschrijver. *Sci Historia.* 1968;10:94-99.
11. Jefferson M. James Parkinson 1755-1824. *BMJ.* 1973;2:601-604.
12. Yahr MD. A physician for all seasons. *Arch Neurol.* 1978;35:185-188.
13. Tyler KL, Tyler HR. The secret life of James Parkinson (1755-1824): the writings of old Hubert. *Neurology.* 1986;36:222-224.
14. Pearce JMS. Aspects of the history of Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1989;52(special suppl):6-10.
15. Herzberg L. An essay on the shaking palsy: reviews and notes on the journals in which they appeared. *Movement Disord.* 1990;5:162-166.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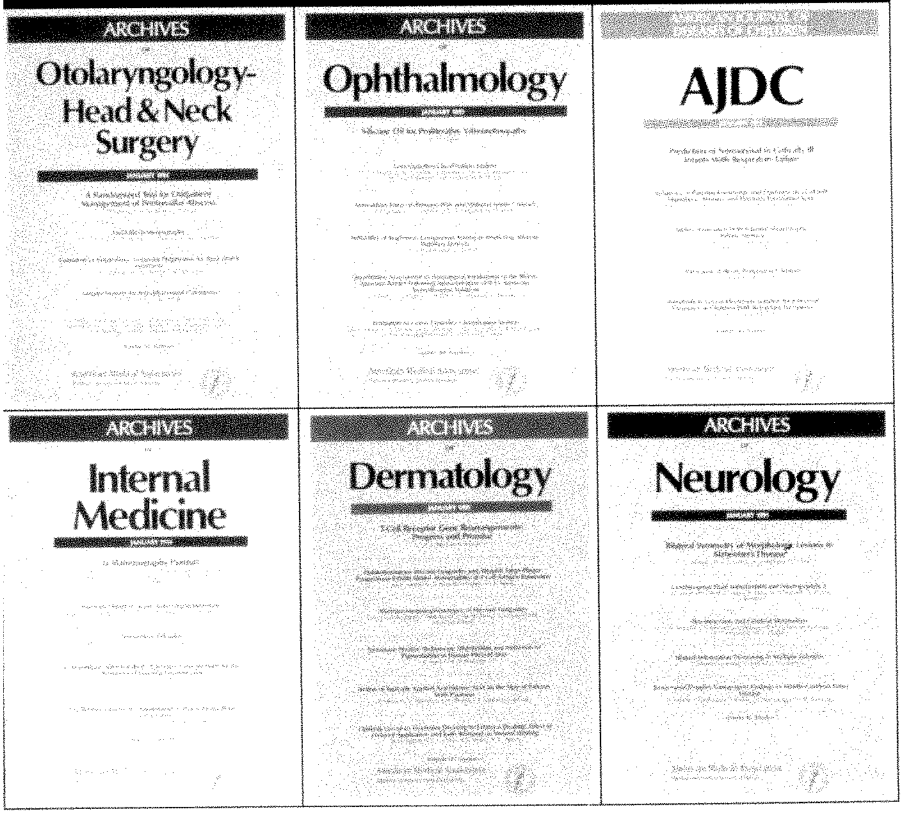
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1. Authors need not be members of the American Neurological Association nor be sponsored by a member. All are welcome to submit abstracts. Acceptance will be based entirely upon quality, without consideration as to status of membership in the ANA or type of presentation. Poster sessions will be expanded; therefore posters are encouraged.
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Observations

Anton's Syndrome in a Patient With Posttraumatic Optic Neuropathy and Bifrontal Contusions

Keith D. McDaniel, MD, Leslie D. McDaniel, MD

• We describe a patient who manifested Anton's syndrome after sustaining head trauma that resulted in optic nerve damage and bifrontal contusions. Denial of monocular blindness, generalized anosognosia, and confabulation were prominent neurobehavioral features. Anton's syndrome is most commonly encountered in patients with bilateral occipital cortex lesions. Patients previously described who demonstrated Anton's syndrome secondary to a peripheral lesion have had an associated delirium or profound dementia. Our case demonstrates that Anton's syndrome may occur in association with blindness from a peripheral lesion, even in the absence of a delirium or significant dementia. We suggest that the bifrontal dysfunction may have been a critical factor in the production of Anton's syndrome. Implications for the role of frontal lobe dysfunction in the genesis of anosognosia and confabulation are discussed.

(*Arch Neurol.* 1991;48:101-105)

Anton's syndrome traditionally refers to the clinical phenomenon of denial of blindness in a patient who has suffered acquired cortical blindness.[1-5] The most common setting of Anton's syndrome is acute bilateral occipital cortex ischemia secondary to posterior circulation insufficiency.

Anton's syndrome is best classified as a subtype of anosognosia, a term originally introduced by Babinski[6] to describe nonrecognition of a specific neurologic deficit. Early descriptions of anosognosia referred primarily to nonrecognition of left hemiplegia in patients with right hemispheric damage.[6-8] Later, anosognosia took on a broader definition to include nonrecognition or denial of hemiplegia, paraplegia, involuntary movements, amnesia, and blindness.[9-18] The degree of anosognosia ranges from minimization of a specific deficit, indifference, or unconcern to lack of recognition and frank denial.

Not all patients with acquired cortical blindness deny their deficit, and there is debate concerning the pathoanatomic locus and neurobehavioral features associated with denial of blindness. Because of its classification as a type of anosognosia, and its occasional co-occurrence with left hemiplegia,[12,19] some investigators have intimated that the anatomic substrate for Anton's syndrome may be the same as for other anosognosias.[12,14] Specifically, the most common and persistent of the anosognosic syndromes are associated with large right hemispheric lesions, producing denial of left hemiplegia, and some authors have suggested that the anosognosic component of cortical blindness may be secondary to right hemispheric dysfunction[20] or to disruption of thalamic connections to right parietal association cortex or visual association cortex.[7,14,20] Others[21] have stated that denial of blindness results when occipital cortex lesions extend beyond calcarine cortex to include visual association cortices (Brodmann's areas 18 and 19).

Disorders of recent memory[18,22,23] are frequently observed in patients with Anton's syndrome. Because cortical blindness is often secondary to posterior circulation insufficiency, inferomedial temporal lobe structures can be similarly affected, thereby producing a disorder of recent memory. The observation that patients with Anton's syndrome confabulate about their visual deficit as well as events subserved by recent memory[13,18,19,22,23] suggests that these patients may also have anosognosia for their memory deficit, thereby resembling patients with Korsakoff's syndrome.[13,23]

Anton's syndrome classically occurs with cortical blindness, and was believed not to occur in cases of blindness from peripheral causes.[24] Although the syndrome is most commonly described in patients with cortical blindness,[1,12,19,21,25-29] there have been numerous case reports of Anton's syndrome occurring in patients with lesions to the anterior visual system, including anterior chamber, optic nerve, and optic chiasm.[13,18,30-34] In all cases of Anton's syndrome associated with anterior visual system lesions, except perhaps one,[22] there has been evidence of profound diffuse cognitive dysfunction.[13,18,30-34] These patients are described as demonstrating evidence of "coarse brain disease" including significant clouding of consciousness, confusion, disorientation, and/or severe dementia. These clinical observations suggest that different mechanisms may be operating in the production of denial of blindness depending on which part of the visual system has been damaged. Geschwind[18] has suggested that when blindness is secondary to a peripheral lesion, denial of the deficit is more dependent on clouding of consciousness or marked dementia than in Anton's syndrome secondary to central lesions, in which damage to visual association cortex is involved.

We report a case of Anton's syndrome in a patient who sustained head trauma with bifrontal contusions and traumatic optic nerve damage that resulted in monocular blindness. Although some memory impairment was present, at the time of the patient's denial of blindness she evidenced neither a confusional state nor a significant dementia. In this case, the denial of blindness was closely correlated with a more generalized anosognosia and a marked propensity for confabulation.

REPORT OF CASE

A 36-year-old right-handed woman was hospitalized after being hit by a subway, having sat in front of the oncoming car in a suicide attempt. She had a history of de-

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From the Departments of Neurology (Dr K. D. McDaniel) and Psychiatry (Drs K. D. McDaniel and L. D. McDaniel), University of Rochester (NY) School of Medicine and Dentistry.

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pression and alcohol and benzodiazepine abuse, but no known history of psychotic symptoms or cognitive impairment. The patient sustained an open, depressed, right anterior frontal skull fracture, multiple maxillary and ethmoid fractures, a right orbital blowout fracture, and pelvic and right lower-extremity fractures. She had initially been found unconscious, but on admission was awake and alternately lethargic and combative, disoriented to place, inconsistently able to answer simple questions, and able to follow only simple commands. Her vital signs were stable. Neurologic examination on admission revealed complete ophthalmoplegia of the right eye with minimal exodeviation; the right pupil was dilated (8 mm), without direct or consensual response to light. Visual acuity examination of the right eye revealed no light perception, and the patient did not respond to visual threat. Examination of the left eye revealed intact direct pupillary light response, visual acuity, and extraocular movements, but absent consensual pupillary light response. The patient was able to move all extremities to command, and plantar responses were flexor.

The blood alcohol level on admission was 157 mg/dL, and the remainder of the toxicology screen was negative.

Computed tomographic head scan on admission demonstrated bilateral frontal fractures extending into the right maxillary sinus and cribriform plate and into the frontal and ethmoidal sinuses bilaterally. There was a fracture through the medial wall of the right orbit, with multiple bone fragments in the right orbit noted near the optic nerve, which appeared edematous. Bilateral hemorrhagic frontal contusions were evident.

The day of admission the patient underwent a craniotomy with subtotal evacuation of bifrontal hematomas, removal of bone fragments, dural repair, and elevation of the depressed skull fracture. Postoperative computed tomographic scans (Figs 1 through 8) showed bilateral frontal contusions with edema, fracture of the right sphenoid wing, and multiple maxillary sinus, right medial orbital, nasal, and frontal fractures. There was evidence of clinoid and posterior sphenoid fractures at the right optic canal and possible hemorrhage or a bone fragment in the right optic nerve.

During postoperative days (PODs) 2 through 7, the patient was awake, intermittently agitated and lethargic, and able to follow simple commands, but no formal mental status testing was performed. She was treated with morphine sulfate (40 to 80 mg/d), midazolam (10 to 35 mg/d), diphenhydramine hydrochloride (50 mg/d), and phenytoin (300 mg/d). Her neurologic examination revealed ophthalmoparesis of the right eye, a right afferent pupillary defect, and no demonstrable vision in the right eye. The right-sided blindness was thought to be secondary to compression or transection of the right optic nerve; and the ophthalmoparesis, to retro-orbital edema. Right ophthalmoparesis was present until POD 8, when full eye movement returned.

On POD 8, psychiatric consultation was requested because of agitation and increasingly disorganized and impulsive behavior. The patient had had tachycardia over the previous several days, but her blood pressure was normal and there was no tremor or nystagmus. On mental status examination, the patient was oriented to year and month but not to day or location. She was distractable and had decreased ability to focus attention (digit span: five forward and none in reverse). Recent memory was impaired, as judged by her inability to recall any of four words after 5 minutes. Language was fluent but disorganized with marked perseveration and confabulation. The patient stated that she was at her sister's house and when confronted with evidence of the hospital surroundings, replied: "Oh, that peroxide and needles are my sister's. She has a skin problem...." She spontaneously reported previous fictitious conversations with staff members. Although both her legs were in casts and her right leg was in traction, she completely denied any problems with her legs. The patient was not fully cooperative with cognitive testing; however, the most prominent aspects of her examination were the disturbance of recent memory; striking spontaneous confabulation about her environment, relationships to hospital staff, and her injuries; and complete denial of all aspects of her illness. The magnitude of these abnormalities were out of proportion to her attentional deficit.

Although the neurobehavioral examination suggested bifrontal and temporal dysfunction, there was evidence of a component of mild delirium, presumed secondary to multiple factors including post-head trauma, postcraniotomy, and morphine and/or benzodiazepine intoxication. Over the next 2 days, with a decrease in the morphine sulfate dosage from 80 mg/d to 6 to 10 mg/d, and discontinuation of midazolam, the patient's agitation, disorientation, and attentional disturbance decreased markedly. On POD 11, the patient was oriented to the date, city, and hospital, but she confabulated about the specific name of the hospital. Her attention span was improved (six digits forward and three in reverse). Language examination revealed normal comprehension, repetition, and naming, but decreased word fluency (word-list generation: five animals in 1 minute). Ideomotor praxis, double-digit calculations, and constructional ability were intact. Recent and remote verbal memory remained impaired. Her interpretations of idioms and proverbs were concrete. Her ability to do frontal motor tasks (Luria hand sequence, alternating sequences, and reciprocal programs) was impaired. She showed paranoid ideation, thinking that the nursing staff was attempting to harm her. Neurologic examination revealed no paresis, symmetric testable reflexes, and normal sensory examination, with no extinction to double simultaneous tactile stimulation. The results of the visual acuity examination were unchanged from POD 8, and continued to show that the patient had no light perception or response to visual threat in her right eye.

At this time (POD 11) the patient continued to demonstrate denial of her illness and prominent confabulation. Although she was blind in her right eye (on six separate trials of varying numbers of fingers held up to each eye separately with the opposite eye occluded, the patient answered six times incorrectly on the right and six times correctly on the left), she denied the visual defect. She offered erroneous answers, stating that she could see, and gave numerous excuses for mistakes made (lighting, headache, angle of the bed; eg, "No, I can see it. I just have a headache...."). She also continued to deny other aspects of her illness. For example, when asked about her leg sling, she replied: "That's not a leg sling, that's an outfit for work; it's a cape. There's nothing wrong with that leg.... I'm in the hospital for a miscarriage.... It's nothing really visible. The doctors are just trying to compare the two legs."

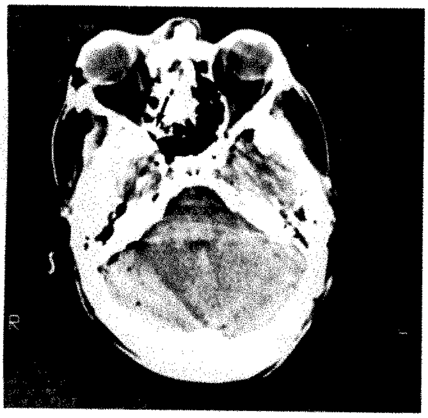
On POD 14, vision in the right eye improved, with evidence of some light perception and accurate finger counting in the superior field of the right eye. At this time the patient began to acknowledge her visual deficit stating, "I can't see very well in that eye." Her recent memory also appeared improved at this time (one out of three words recalled after 5 minutes). Denial of her illness and confabulation about her relationships with staff members and her medical condition continued but were less marked. Over the next 2 weeks her recent memory deficit, denial of illness, and confabulation gradually resolved. By POD 30, the patient demonstrated full orientation and normal attention and concentration abilities. Her long-term memory was improved, and her visual and recent verbal memory were intact (able to recall three out of three words after 5 minutes). She demonstrated good verbal comprehension, naming, and repetition but continued to show decreased word fluency (six animals in 1 minute). Constructional ability and calculations were intact. Although the frontal motor tasks were accurately performed, her thinking remained concrete. She only rarely confabulated about her relationships with staff members.

The behavioral syndrome described on POD 11 persisted and included inappropriate, disinhibited behavior with evidence of poor insight and social judgment, extreme irritability, affective lability, verbal disinhibition with frequent threats and occasional physical abuse toward nursing staff, and paranoid ideation. The patient's family stated that these behaviors had not been present at any time prior to the hospitalization.

On POD 42, computed tomographic head scan showed bifrontal encephalomalacia with increased size of the anterior horns of the lateral ventricles and a questionable bone fragment extending into the superior aspect of the right orbit. Electroencephalography showed normal alpha activity posteriorly, with intermittent bilateral temporal and posterior temporal slowing in the theta and, at times, delta frequencies.

COMMENT

This is the first detailed published case of Anton's syndrome associated with blindness from an anterior visual



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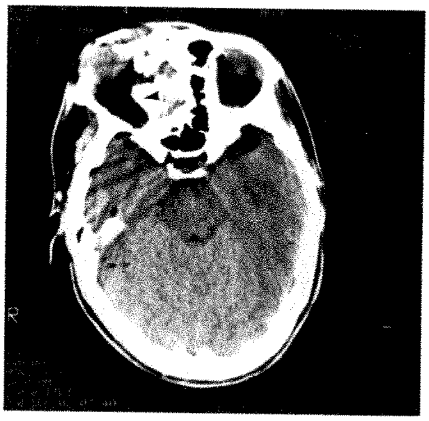

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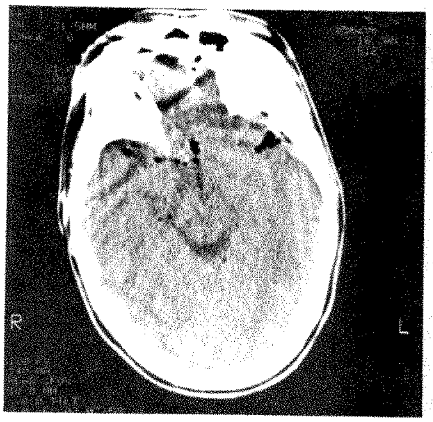

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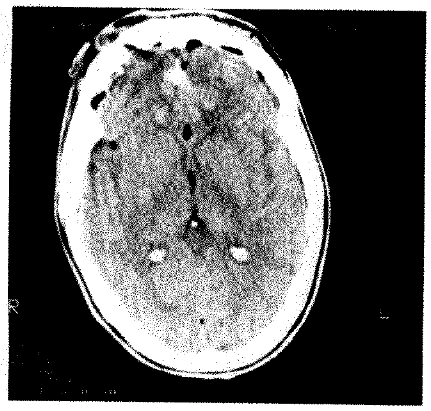

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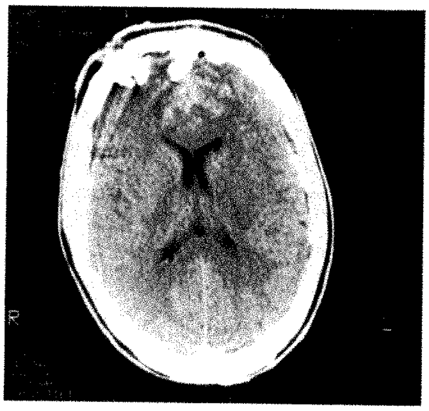

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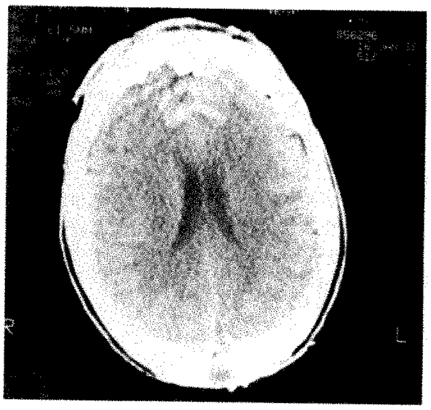

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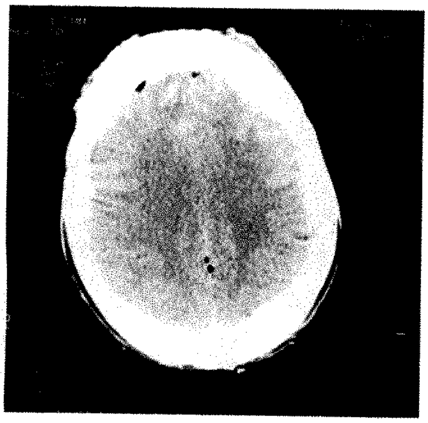

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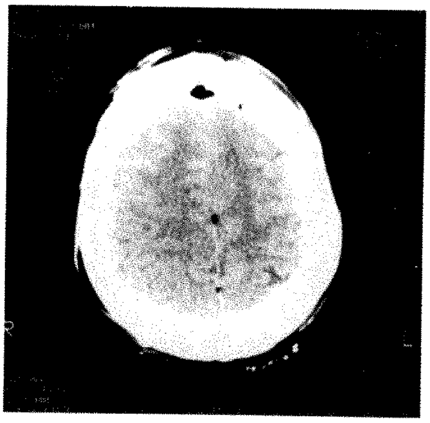

Figure 8.

Figs 1 through 8.—Postoperative noncontrast computed tomographic head scan performed the day of admission demonstrating bilateral frontal contusions, disruption of the integrity of the right optic foramen from posterior sphenoid fractures (arrow, Fig 1), and possible hemorrhage or bone fragment adjacent to right optic nerve (arrowhead, Fig 2). Figure 1. Figure 2. Figure 3. Figure 4. Figure 5. Figure 6. Figure 7. Figure 8.

lesion occurring in the absence of a confusional state or significant dementia. Stuss and Benson[22] reported a remarkably similar case of bifrontal contusions and blindness from optic neuropathy, with unconcern and minimization of the visual deficit. Their brief description stated that the patient was "alert and fully oriented"; however, more detailed neuropsychological testing was not reported. The patient we describe demonstrated numerous neurobehavioral abnormalities, including an orbitofrontal lobe syndrome (disinhibited, impulsive behavior, inappropriate affect, emotional lability, irritability, poor judgment and insight, distractibility, and unconcern),[35] impaired frontal motor tasks, verbal memory disorder, confabulation, and denial of illness, including Anton's syndrome. Language (except for diminished word-list generation), ideomotor praxis, visuoconstructive and calculation abilities, and visual memory were all unaffected. At the time the patient manifested Anton's syndrome, findings of the elementary neurologic examination were normal, with the exception of the noted blindness of the right eye and the absence of right direct pupillary response.

Two prominent features of the current case are the patient's generalized anosognosia and the dramatic spontaneous confabulatory responses, which persisted beyond the acute confusional state. Although confabulation is most often encountered in the acute stages of Korsakoff's syndrome,[36] it is also seen in patients with amnesia resulting from a variety of causes.[35] As not all patients with amnesia demonstrate confabulation, a concomitant neurobehavioral alteration or focal anatomic lesion may be necessary for the production of confabulation. Although some degree of memory impairment is probably necessary, there is evidence that confabulation is additionally dependent on frontal lobe dysfunction manifesting as perseveration, lack of verbal inhibition, and poor self-monitoring.[37-39] Some investigators have speculated that the confabulation demonstrated by patients with Korsakoff's syndrome is an indication of impairment of cognitive functions in addition to memory.[40] The poor strategy formation in problem-solving tasks demonstrated by these patients[41] suggests disruption of frontal lobe functioning. The bulk of evidence indicates that confabulation is encountered most commonly in patients with memory disorders when there is an associated confusional state or bifrontal dysfunction.[38,39,42-44] Some investigators distinguish between provoked confabulation as a normal response to impaired memory and spontaneous or fantastic confabulation as indicative of frontal dysfunction occurring in conjunction with an underlying memory disorder.[38,43,44] Additionally, there is speculation that deficits in frontal lobe-dependent, self-monitoring functions may also be involved in producing anosognosic syndromes.[22]

Many observers have noted a close relationship between the tendency toward confabulation and anosognosia.[5,18,22,23,40] The intricacies of these phenomena have recently been elaborated by Fisher,[23] who suggests that "unawareness is a necessary precondition for confabulation." Importantly, in virtually all cases of both central and peripheral Anton's syndrome described, there is mention of confabulation, in relation both to the visual deficit itself and to other aspects of the patient's clinical state.[13,18,19,21,25] In our patient, confabulation was closely associated with generalized anosognosia, both of which resolved almost simultaneously. It may be that confabulation is a requisite accompaniment to Anton's syndrome regardless of the site of visual system damage.

Our patient demonstrated a memory disorder with electroencephalographic evidence of bitemporal dysfunction and a clinical frontal lobe syndrome with bifrontal structural lesions demonstrated on computed tomographic scan. We suggest that the bitemporal and bifrontal dysfunctions were essential in the production of the patient's confabulation and anosognosia and that these features, in conjunction with the visual defect, produced Anton's syndrome. The patient's memory disorder, confabulation, and anosognosia resolved together, although the frontal lobe behavioral syndrome persisted. With regard to the patient's anosognosia, it is important to note that right parietal function was found to be normal based on visuoconstructive abilities, neurologic examination, computed tomographic scan, and electroencephalography.

As noted in the case description, resolution of the denial of monocular blindness occurred as the patient's vision began to return. The remaining anosognosic features persisted and then subsequently cleared with resolution of the confabulation and memory disorder, suggesting an important interaction among these variables. However, it is important to note that the anosognosia and confabulation occurred when edema from the acute frontal contusions would have been maximal. Independent of improvement of the patient's memory function, it is possible that reduction of frontal edema was a contributing factor in the resolution of both the confabulation and the anosognosia.

This case demonstrates that denial of blindness in cases of anterior visual system lesions does not necessarily require a confusional state or severe dementia, as suggested in previous reports. Instead, we suggest that the interaction of a memory deficit with the inability to critically self-monitor responses due to frontal dysfunction was sufficient to produce denial of blindness secondary to a peripheral lesion. This case provides supporting evidence for the hypothesis perhaps initially proposed by Bychowski[45] and elaborated by Stuss and Benson[22] that frontal lobe dysfunction may be a critical factor in nonrecognition or denial of a deficit, including blindness resulting from peripheral causes.

References

1. Anton G. Ueber die Selbstwahrnehmung der Herderkrankungen des Gehirns durch den Kranken bei Rindenblindheit und Rindentaubheit. *Arch Psychiatr.* 1899;32:86-127.

2. Von Monakow A. Experimentelle und pathologischanatomisch Untersuchungen über die Beziehungen der sogenanten Sehspare zu den infracorticalen Opticuscentren und zum Nervus opticus. *Arch Psychiatr.* 1885;16:151-199.

3. Dejerine, Vialet. Sur un cas de cécité corticale diagnostiquée pendant la vie et confirmée par l'autopsie. *C R Soc Biol.* 1893;11:983-997.

4. Rossolimo G. Ueber Hemianopsie und einseitige Ophthalmoplegie Vasculären Ursprungs. *Neurol Centralbl.* 1896;15:626-637.

5. Lunz C. Zwei Falle von korticaler Seelenblindheit. *Dtsch Med Wochenschr.* 1897;1:381-393.

6. Babinski J. Contribution à l'étude des troubles mentaux dans l'hémiplégia organique cébérale (anosognosie). *Rev Neurol (Paris).* 1914; 22:845-884.

7. Peotzl O. Ueber Störungen der Selbstwahrnehmung bei linkeseitiger Hemiplegie. *Z Neurol Psychiatr.* 1924;93:117-168.

8. Barkman A. De l'anosognosie dans l'hémiplégie cérébrale: contribution clinique à l'étude de ce symptome. *Acta Med Scand.* 1925;62:213-254.

9. Lhermitte J. *L'image de Notre Corps.* Paris, France: Nouvelle Revue Critique; 1939.

10. Olsen CW, Ruby C. Anosognosia and autotopagnosia. *Arch Neurol Psychiatry.* 1941;46:340-344.

11. Gerstmann J. Problem of imperception of disease and of impaired body territories with organic lesions. *Arch Neurol Psychiatry.* 1942; 48:890-913.

12. Weber FP. Agnosia of hemiplegia and of blindness after cerebral embolism. *Lancet.* 1942;1:44-46.

13. Redlich FC, Dorsey JF. Denial of blindness by patients with cerebral disease. *Arch Neurol Psychiatry.* 1945;53:407-417.

14. Sandifer PH. Anosognosia and disorders of body scheme. *Brain.* 1946;69:122-137.

15. Weinstein EA, Kahn MA. The syndrome of anosognosia. *Arch Neurol Psychiatry.* 1950; 64:772-791.

16. Cohn R. Anosognosia. *Q Rev Psychiatr Neurol.* 1948;3:83-92.

17. Critchley M. *The Parietal Lobes.* New York, NY: Hafner Press; 1953.

18. Geschwind N. Disconnexion syndromes in animals and man. *Brain.* 1965;88:237-294, 585-643.

19. Raney AA, Nielsen JM. Denial of blindness (Anton's symptom): two clinical cases. *Bull L A Neurol Soc.* 1942;7:150-151.

20. Damasio AR. Disorders of complex visual processing: agnosias, achromatopsia, Balint's syndrome, and related difficulties in orientation and construction. In: Mesulam MM, ed. *Principles of Behavioral Neurology.* Philadelphia, Pa: FA Davis Co Publishers; 1985:259-288.

21. Cusumano JV, Fletcher JW, Patel BK. Scintigraphic appearance of Anton's syndrome. *JAMA.* 1981;245:1248-1249.

22. Stuss DT, Benson DF. *The Frontal Lobes.* New York, NY: Raven Press; 1986.

23. Fisher CM. Neurologic fragments, II: remarks on anosognosia, confabulation, memory, and other topics; and an appendix on self observation. *Neurology.* 1989;39:127-132.

24. Magitot A, Hartmann E. La cécité corticale. *Bull Soc Ophtalmol Paris.* 1926;38:427-440.

25. Ter Braak JWG, Schenk VWD, Van Vliet AGM. Visual reactions in a case of long-standing cortical blindness. *J Neurol Neurosurg Psychiatry.* 1971;34:140-147.

26. Adams RD, Victor M. *Principles of Neurology.* 4th ed. New York, NY: McGraw-Hill International Book Co; 1989.

27. Bergman PS. Cerebral blindness. *Arch Neurol Psychiatry.* 1957;78:568-584.

28. Symonds C, Mackenzie I. Bilateral loss of vision from cerebral infarction. *Brain.* 1957; 80:416-455.

29. Lantos G. Cortical blindness due to osmotic disruption of the blood brain barrier by angiographic contrast material: CT and MRI studies. *Neurology.* 1989;39:567-571.

30. Tunero J. Ein Fall mit Anton's Symptom. *Psychiatr Neurol Japon.* 1931;41:679-690.

31. Redlich E. Bonvicini G. Weitere klinische und anatomische Mitteilungen über das Fehlen derWahrnehmungdereigenenBlindheitbeinHirnkrankheiten. *Neurol Centralb.* 1911;30:277-301.

32. Albrecht O. Drei Falle mit Anton's Symptom. *Arch Psychiatr.* 1918;59:883-941.

33. Angelergues R, de Ajuriaguerra J, Hécaen

H. La négation de la cécité au cours des lésions cérébrales. *J Psychologie.* 1960;57:381-404.

34. Swartz BE, Brust JCM. Anton's syndrome accompanying withdrawal hallucinosis in a blind alcoholic. *Neurology.* 1984;34:696-673.

35. Cummings JL. *Clinical Neuropsychiatry.* New York, NY: Grune & Stratton; 1985.

36. Victor M, Adams RD, Collins GH. *The Wernike-Korsakoff Syndrome and Related Neurologic Disorders due to Alcoholism and Malnutrition.* 2nd ed. Philadelphia, Pa: FA Davis Co Publishers; 1989.

37. Mercer B, Wapner W, Gardner H, Benson DF. A study of confabulation. *Arch Neurol.* 1977;34:429-433.

38. Kapur N, Coughlan AK. Confabulation and frontal lobe dysfunction. *J Neurol Neurosurg Psychiatry.* 1980;43:461-463.

39. Shapiro BE, Alexander MP, Gardner H, Mercer B. Mechanism of confabulation. *Neurology.* 1981;31:1070-1076.

40. Hécaen H, Albert M. *Human Neuropsychology.* New York, NY: John Wiley & Sons Inc; 1978.

41. Oscar-Berman M, Goodglass H, Chirlow DG. Perceptual laterality and iconic recognition of visual materials by Korsakoff patients and normal adults. *J Comp Physiol Psychol.* 1973; 82:316-321.

42. Berlyne N. Confabulation. *Br J Psychiatry.* 1972;120:31-39.

43. Stuss DT, Alexander MP, Lieberman A, Levine H. An extraordinary form of confabulation. *Neurology.* 1978;28:1166-1172.

44. Kopelman MD. Two types of confabulation. *J Neurol Neurosurg Psychiatry.* 1987;50:1482-1487.

45. Bychowski Z. Ueber das fehlen der Wahrnehmung der eigen Blindheit bei zwei Kriegsverletzen. *Neurol Centralbl.* 1920;106:354-357.

Pupil-Sparing Oculomotor Nerve Palsy due to Midbrain Infarction

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• Vasculopathic oculomotor nerve palsies with pupillary sparing are thought to be due to ischemic damage to the nerve in the subarachnoid space or the cavernous sinus. We present two cases of patients with isolated pupil-sparing oculomotor nerve palsies due to midbrain infarcts. Focal ischemic midbrain lesions should be considered in cases of pupil-sparing oculomotor nerve palsies.

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Infarction of the oculomotor nerve causes pupil-sparing oculomotor palsies associated with diabetes mellitus or hypertension. At present, the favored site of the infarction is the peripheral portion of the nerve, rather than the intra-axial portion. Intra-axial lesions causing pupil-sparing oculomotor palsies are rare in the literature.[1] The association of a hemiparesis, rubral tremor, or sensory loss with the oculomotor palsy places the lesion in the midbrain. In 1987, Hopf and Gutmann[2] postulated the intra-axial location of isolated pupil-sparing palsy based on studying the masseter reflex. The mesencephalic tract of the trigeminal nerve moderates the masseter reflex. This tract extends up to the level of the oculomotor nucleus and lies dorsolateral to the nucleus. The authors hypothesized that a lesion affecting the oculomotor nerve in the midbrain also could affect the masseter reflex. Using electrophysiologic recording of masseter reflex responses, they found depressed responses ipsilateral to the oculomotor palsy in several patients. In support of this hypothesis, we report two cases of patients with isolated pupil-sparing oculomotor palsy with magnetic resonance imaging scan substantiation of mesencephalic lesions.

REPORT OF CASES

Case 1.—A 23-year-old previously healthy woman presented with the abrupt onset of severe, throbbing retro-orbital headache on the left side. An hour later, she noticed oblique diplopia and ptosis of the left eyelid. Prior to reaching the hospital, she experienced tingling around the mouth on the right side associated with slurred speech and clumsiness of her right hand. By the time she reached the emergency department, the paresthesias and dysarthria had resolved. Her medical history was unremarkable except for the use of oral contraceptive agents for 2 years. The family history was positive for migraine in her mother and maternal grandmother.

Examination on admission revealed only a complete oculomotor palsy with total sparing of the pupil. No speech disturbance or other focal neurologic signs were evident. Results of radiologic studies, including a computed tomographic scan of the head with and without contrast, and cerebral angiography of the carotid and basilar arterial systems were normal. Results of blood tests revealed negative serologic test results for syphilis, a Westergren sedimentation rate of 15 mm/h, a negative antinuclear antibody and rheumatoid factor, and normal complement function. Screening for diabetes, hypertension, and heart disease was also negative. The spinal fluid was normal with a cell count of 4×10^6 leukocytes per liter and 5×10^6 erythrocytes per liter. The cerebrospinal fluid protein level was 0.28 g/L and the glucose level was 2.9 mmol/L. Cerebrospinal fluid VDRL was negative, and the IgG levels, myelin basic protein, and oligoclonal bands were all within normal limits. Results of an edrophonium test were also negative. A magnetic resonance imaging scan revealed a lesion in the left midbrain suggestive of an infarct (Fig 1). The abnormal signal was located primarily in the fascicular portion of the left third nerve in the caudal portion of the midbrain. The diagnosis of complicated migraine was made. She stopped taking her oral contraceptives and had gradual improvement of her ptosis and ocular motility, with total resolution after 6 months. No evidence of acquired oculomotor synkinesis was present at the time.

Case 2.—A 78-year-old woman with insulin-dependent diabetes mellitus presented with the painful abrupt onset of horizontal diplopia. Examination revealed a complete third-nerve palsy of the left eye with total sparing of the pupil. A computed tomographic scan of the head was normal. The magnetic resonance imaging scan revealed a lesion in the left midbrain in the fascicular portion of the third nerve (Fig 2).

Masseter reflex latency (3 days after onset) was determined by stimulating the jaw mechanically with a reflex hammer containing a piezo-electric element to trigger the oscilloscope sweep. The reflex response was recorded simultaneously by surface electrodes over both masseter muscles (recording electrodes) and the lateral edge of the orbits (reference electrodes). The reflex latency was 8.7 milliseconds on the left side and 7.9 milliseconds on the right side (normal side-to-side difference, <0.5 milliseconds). Two weeks later the latencies were normal at 8.1 milliseconds bilaterally.

COMMENT

Both of our patients had apparent ischemic pupil-sparing oculomotor

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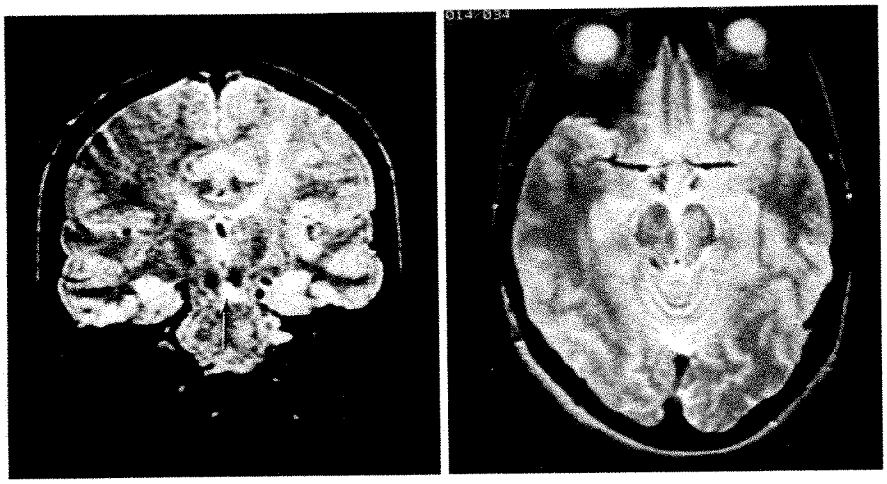

Fig 1.—Left, Case 1. Coronal T_2-weighted magnetic resonance imaging reveals an area of increased signal in the midbrain located left of the midline and caudal to the red nucleus. Right, Case 1. Axial T_2-weighted magnetic resonance imaging reveals an area of increased signal on the left in the region of the third-nerve fascicle.

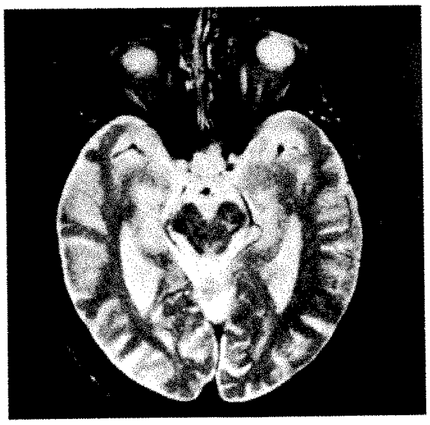

Fig 2.—Case 2. Axial T_2-weighted magnetic resonance imaging at the midbrain level reveals an area of increased signal on the left side adjacent to the cerebral peduncle extending into the third-nerve fascicle.

palsy unassociated with other neurologic abnormalities on examination, and had demonstrable midbrain lesions by magnetic resonance imaging. The prolonged masseter reflex latency in patient 2 also supports an intra-axial lesion. These cases challenge the present tenets regarding isolated pupil-sparing oculomotor lesions of ischemic origin. Three autopsy studies of diabetic patients with pupil-sparing oculomotor palsy provide the basis for the current theory about the location of the anatomic lesion.[3-5] Examination of the affected nerves revealed abnormalities in the cavernous sinus portion of the nerve,[3,4] or just after exiting the midbrain in the subarachnoid space.[5] Microscopic sections revealed destruction of myelin, narrowing of the vasa nervorum, and axonal damage. None of the autopsy studies found the arterial occlusion thought to casue the lesion. The authors found sparing of the peripherally located pupillomotor fibers in comparison with the core of the nerve. They felt that pupillary sparing was based on end-arterial ischemia to the center of the nerve and the relative resistance of the small unmyelinated pupillary fibers to ischemia.

In our cases the lesions diagnosed by magnetic resonance imaging are in the fascicular portion of the nerve. The fibers of the oculomotor nucleus traverse the midbrain as multiple bundles and course both through and around the red nucleus.[6] The expansion of the red nucleus during embryologic development is thought to cause the spreading of the fibers. Neuroanatomic studies of rats show that the oculomotor rootlets emerge from the brain stem as free rootlets and fuse to become the oculomotor nerve trunk after traveling a short distance in the subarachnoid space.[7] Therefore, a fascicular lesion could theoretically lead to sparing of the pupil or an innervated muscle. In addition, the caudal location of the lesion in patient 1 could explain the pupil sparing by not involving fibers from the more superiorly located Edinger-Westphal nucleus. Fascicular lesions of the oculomotor nerve have caused other atypical oculomotor palsies.[1,8,9] In 1983, Nadeau and Trobe[1] published two cases of pupil-sparing oculomotor palsy due to midbrain lesions involving the fascicle. These cases differed from ours in that both of the patients had additional neurologic findings on examination.

Oculomotor nuclear lesions also cause atypical partial oculomotor palsies. In 1982, Warren et al[10] reported cases of isolated inferior rectus palsies. The authors felt the anatomic lesion was in the oculomotor nucleus. Smith[11] questioned the validity of the hypothesis because no anatomic proof was available. Five years later an autopsy study of a patient with an isolated inferior rectus palsy revealed a solitary metastasis to the apropriate oculomotor nucleus.[12] Magnetic resonance imaging scans revealed the lesion premorbidly.

Focal midbrain lesions can be the basis for isolated pupil-sparing oculomotor palsies, and may be more common than previously thought. Hopf and Gutmann,[13] studying diabetic patients with isolated third-nerve palsies (the majority with pupil sparing), noted that the ipsilateral masseter reflex response was completely or partially absent or the reflex latency was delayed in most of the patients. These findings provide further support for a mesencephalic location for isolated oculomotor palsies. Continuing investigations involving magnetic resonance imaging scans, pathologic examination, and electrophysiological studies are needed to further assess the relative importance of midbrain lesions in the cause of these cases.

References

1. Nadeau SE, Trobe JD. Pupil-sparing in oculomotor palsy: a brief review. *Ann Neurol.* 1983;13:143-148.
2. Hopf HC, Gutmann L. Masseter reflex abnormalities in third-nerve palsies: evidence for a mesencephalic lesion. *Neurology.* 1987;37(suppl 1):115.
3. Dreyfus PM, Hakin S, Adams RD. Diabetic ophthalmoplegia: report of a case, with postmortem study and comments on vascular supply of human oculomotor nerve. *Arch Neurol Psychiatry.* 1957;77:337-349.
4. Asbury AK, Aldredge H, Hershberg R, Fisher CM. Oculomotor palsy in diabetes mellitus: a clinico-pathological study. *Brain.* 1970;93:555-556.
5. Weber RB, Daroff RB, Mackey EA. Pathology of oculomotor nerve palsy in diabetics. *Neurology.* 1970;20:835-838.
6. Truex RC, Carpenter MB. *Human Neuroanatomy.* 6th ed. Baltimore, Md: Williams & Wilkins; 1969:388.
7. Fraher JP, Smiddy PF, O'Sullivan VR. The central-peripheral transitional regions of cranial nerves: oculomotor nerve. *J Anat.* 1988;161:103-113.
8. Fleet WS, Rapcsak SZ, Huntley WW, Waston RT. Pupil-sparing oculomotor palsy from midbrain hemorrhage. *Ann Ophthalmol.* 1988; 20:345-346.
9. Keane JR. Isolated brain-stem third-nerve palsy. *Arch Neurol.* 1988;45:813-814.
10. Warren W, Burde RM, Klingele TC, Roper-Hall G. Atypical oculomotor paresis. *J Clin Neuroophthalmol.* 1982;2:13-18.
11. Smith JL. The 'nuclear third' question. *J Clin Neuroophthalmol.* 1982;2:61-63.
12. Pusateri TJ, Sedwick LA, Margo CE. Isolated inferior rectus muscle palsy from a solitary metastasis to the oculomotor nucleus. *Arch Ophthalmol.* 1987;105:675-677.
13. Hopf HC, Gutmann L. Diabetic third-nerve palsy: evidence for a mesencephalic lesion. *Neurology.* 1990;40:1041.

Congenital Monomelic Hypertrophy With Progressive Myopathy

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• We describe a patient with congenital monomelic hypertrophy who later developed progressive footdrop due to a degenerative myopathy. The clinical, electrophysiologic, and pathologic features of the case are described and compared with those of a previously reported case.

(*Arch Neurol.* 1991;48:107-110)

From the earliest investigation of progressive degenerative disorders of muscles in the mid-19th century, there has been interest in the phenomenon of muscular hypertrophy, or pseudohypertrophy.[1-3] This is usually a symmetrical and generalized process, and associated with progressive muscle weakness. There have been a small number of reports of muscle hypertrophy associated with nerve lesions, such as radiculopathies,[4-6] but usually muscle weakness with hypertrophy (pseudohypertrophy) is a myopathic process. There have also been a few reports of congenital hypertrophy of muscle, connective tissue, and bone restricted to one side or to a single extremity[7-16] and associated with diverse clinical features. One patient with monomelic hypertrophy described by Celesia et al[7] developed a progressive myopathy. We report a second case of congenital monomelic hypertrophy with progressive myopathy, which differs from the case reported by Celesia et al[7] because of the absence of clinical and electromyographic myotonia.

REPORT OF A CASE

At birth, the left leg of our patient was noted to be larger than the right, both in girth and in length. At the age of 11 years, she underwent epiphysiodesis of the left fibula, tibia, and second and third toes and ray deletion and excision of the fifth toe. A biopsy specimen of the tibialis anterior muscle showed chronic myopathic changes (see below). The specimen of the left fifth toe included muscle that showed no abnormality. Soon after this, her parents noted that she had difficulty with the frog kick while swimming, and at the age of 12 years, she developed inability to dorsiflex the left great toe. At the age of 15 years, she underwent a left peroneus longus tendon transplant and debulking and shortening of the first and second toes. A left adductor hallucis muscle biopsy specimen showed chronic myopathic changes similar to those seen in the tibialis anterior muscle specimen. At age 16 years, the patient developed a progressive left footdrop and underwent electrophysiologic studies (see below), computed tomography, and magnetic resonance imaging of the thoracolumbar region, all of which revealed no abnormalities. By the age of 20 years, the left footdrop had progressed, and the patient complained of left hip and leg pain on walking. Subsequent electrophysiologic studies and magnetic resonance imaging of the legs were performed (see below).

A physical examination performed when the patient was 20 years old showed her left leg to be 1 inch longer than her right leg. The circumference of the left leg and the size of the left foot were increased compared with the right (Fig 1). Her left shoe was size 8, and her right shoe was size 6. The muscle bulk was increased throughout the left leg, with the exception of the left tibialis anterior muscle, which was of normal bulk. There was no hypertrophy of any other parts of the body. There was a left footdrop with varus deformity and contracture of the left tendo achillis. There was no observable contraction of the left tibialis anterior, peroneus longus, and extensor hallucis longus muscles. The left triceps surae muscle, hip adductors and abductors, and extensor digitorum brevis muscle were slightly weak on toe walking. The strength of all other muscles appeared normal. The right knee and ankle jerks were 2+, the left knee jerk was trace, and the left ankle jerk was 1+. Plantar responses were flexor. There was diminution of pinprick sensation over the upper lateral aspect of the left shin that had been present since the prior knee surgery.

INVESTIGATIONS

The patient's serum creatine kinase level was 165 IU (normal, 21 to 80 IU), with an MB fraction of 7% and a BB fraction of 0%. Other hematologic and biochemical test results were normal.

Peripheral Electrophysiologic Studies

When the patient was 16 years old, findings of motor conduction studies in the left peroneal nerve, terminal latency, F-wave latency, and amplitude of the maximal evoked-action potential were normal, as was the left sural sensory nerve action potential.

Electromyography (EMG) of the left tibialis anterior muscle showed profuse fibrillation potentials and positive sharp waves, complex repetitive discharges (CRDs), and numerous early-recruited brief-duration motor unit action potentials. Similar but lesser changes were seen in the left peroneus longus and vastus lateralis muscles. The left gastrocnemius muscle, the muscles in the right lower limb, and the paraspinal muscles showed no abnormalities. Single fiber EMG of the left tibialis anterior muscle revealed an increased fiber density of 2.05 (normal, 1.57 ± 0.22),[17] with several pairs exhibiting increased jitter and blocking.

When the patient was 19 years old, findings of motor conduction studies in the left peroneal and tibial nerves were entirely normal, including peroneal nerve conduction across the fibular head. Electromyography of the left tibialis anterior and extensor hallucis longus muscles showed increased insertional activity, fibrillation potentials and positive sharp waves, CRDs, and no voluntarily activated motor units. The left peroneus longus muscle showed very similar changes, with very-brief-duration low-amplitude motor unit potentials. Lesser degrees of myopathic change were seen in the left extensor digitorum brevis and lateral gastrocnemius muscles. The left biceps femoris muscle showed no abnormality.

When the patient was 20 years old, EMG of the right tibialis anterior, gastrocnemius, and extensor digitorum brevis muscles revealed no abnormalities.

Muscle Biopsy Findings

When the patient was 11 years old, paraffin-embedded sections of the left tibialis anterior muscle showed extensive myopathic changes with areas of muscle fiber hypertrophy, an increased proportion of fibers with internal nuclei, and many small degenerating and regenerating muscle fibers embedded in connective tissue. A few foci of chronic inflammatory cells were seen without a perivascular distribution.

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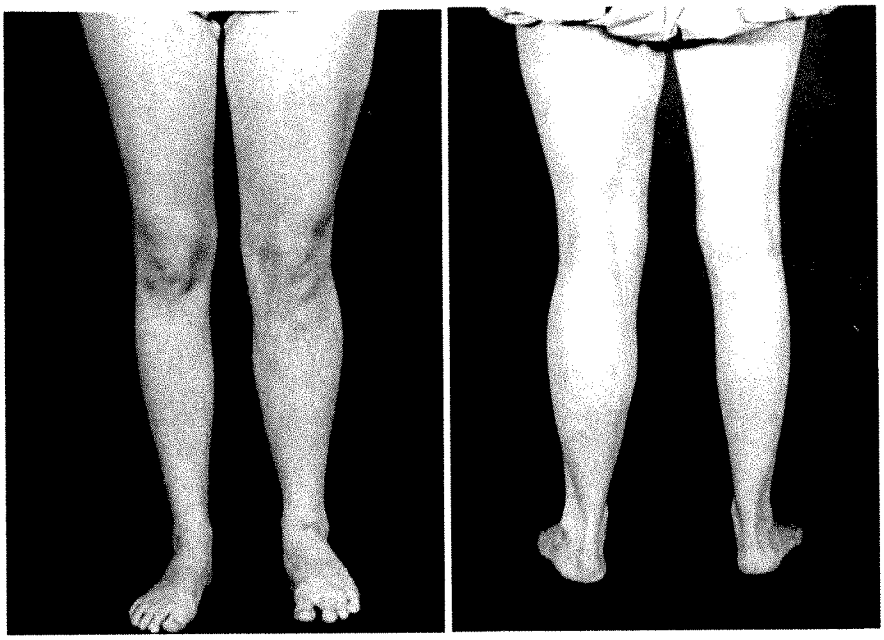


Fig 1.—Front (left) and back (right) views of patient's legs showing the increase in girth of the entire left leg.

When the patient was 15 years old, cryostat sections of the left adductor hallucis muscle showed disseminated necrotic and regenerating fibers, with foci of interstitial inflammatory cells. There were clumps of regenerating fibers and minor changes suggesting fiber-type grouping. There was a considerable increase of interstitial connective tissue, fiber splitting, and fiber hypertrophy (Fig 2).

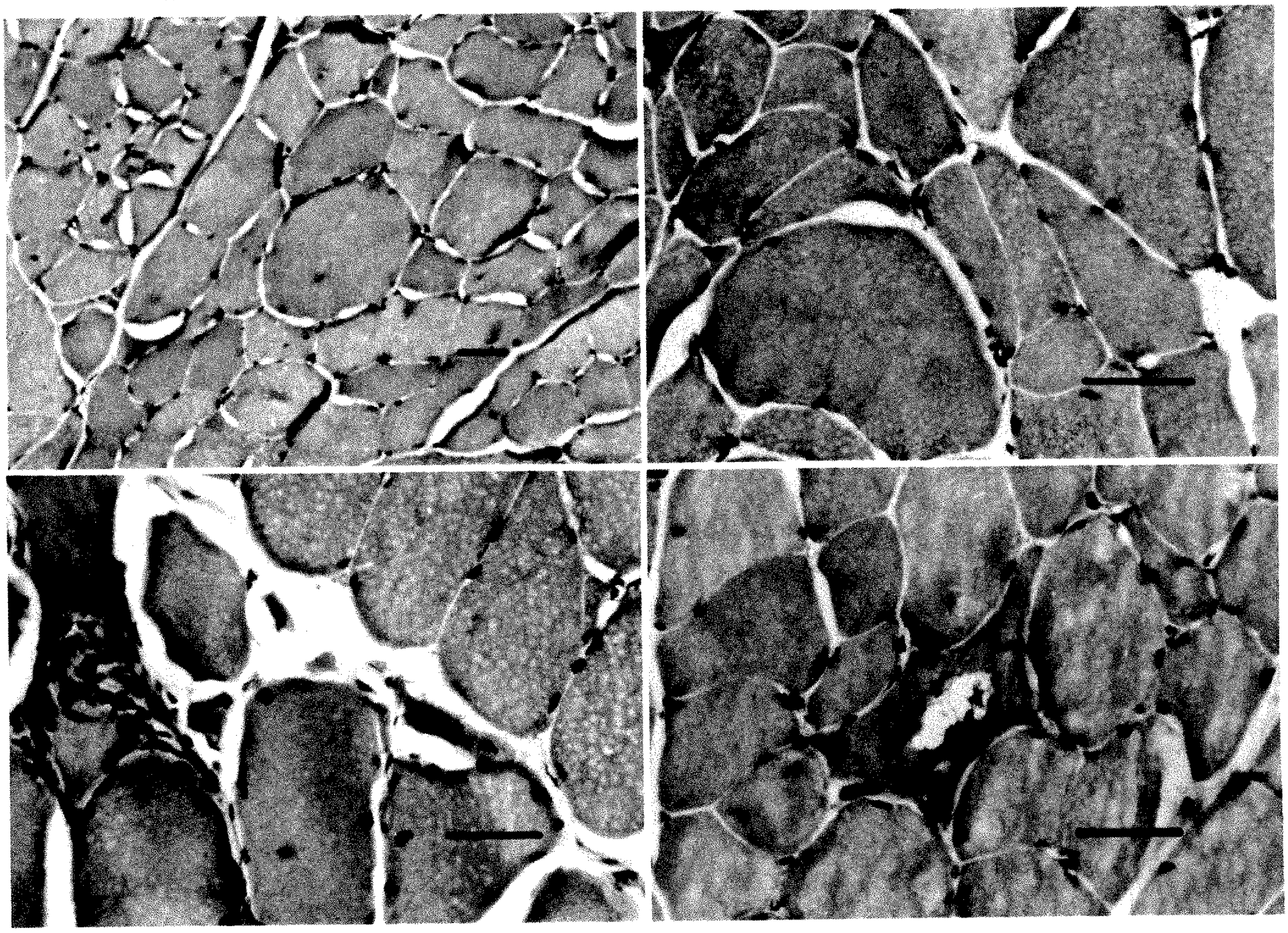
Magnetic Resonance Imaging

When the patient was 18 years old, magnetic resonance imaging showed considerable hypertrophy of the muscles of the left leg including the glutei (Fig 3). The left tibialis anterior muscle, the peroneal muscles, and the deep part of the medial gastrocnemius muscles were atrophic, with areas of abnormal increased signal intensity.

COMMENT

A diagnosis of the rare condition of monomelic hypertrophy requires en-

Fig 2.—Cryostat sections of left adductor hallucis muscle at age 15 years. There is considerable variation in fiber size and shape, with both rounded and angular atrophic fibers (top left) occasional hypertrophic fibers (top right), necrotic fibers (bottom left), and rimmed vacuoles (bottom right) (hematoxylin-eosin; bars = 50 μm).



largement in both bulk and length of all the elements (bones, muscles, and connective tissue) in one limb. There are many causes of this syndrome. Monomelic hypertrophy is most frequently idiopathic, although it can be secondary to local causes such as a proximal arteriovenous malformation of the limb,[18] angiomatosis,[19] or nerve trauma.[20] It has also been associated with neurofibromatosis[9] and Wilms' tumor.[14] A contralateral hemiatrophy, resulting from congenital cerebral lesions such as a porencephalic cyst, must not be misinterpreted as hemihypertrophy of the normal side.

To our knowledge, monomelic hypertrophy and a progressive monomelic myopathy have been associated only in our case and that of Celesia et al.[7] Celesia and colleagues described a woman with right lower-extremity monomelic hypertrophy present from birth, who at the age of 12 years developed progressive footdrop and weakness of the right hip flexors. In both cases, electrophysiologic and pathological studies revealed a typical myopathy. The patient of Celesia and colleagues had spontaneous and percussion myotonia restricted to the affected quadriceps femoris muscle and "bursts of high-frequency discharges to electrode movement and after volitional contraction, characteristic of myotonia," on EMG. Myotonia was absent in our case, although there was considerable membrane irritability with CRDs.

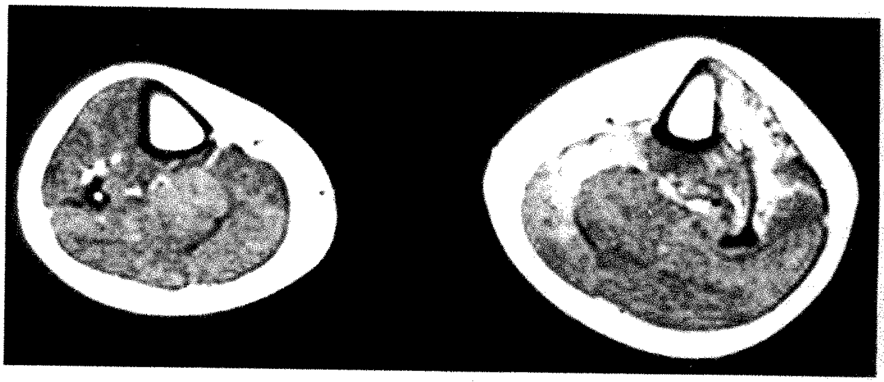


Fig 3.—Magnetic resonance imaging (repetition time, 300 milliseconds; echo time, 30 milliseconds). Coronal view of the legs at midcalf level showing the increase in bulk of most of the muscles on the left, and patchy increased signal in the atrophic tibialis anterior muscle, the peroneal muscles, and the deep part of the medial gastrocnemius muscles.

True myotonic discharges are characterized as repetitive discharges at rates of 20 to 80 Hz of either biphasic spike potentials of less than 5-millisecond duration or positive waves of 5- to 20-millisecond duration, recorded with an EMG needle after voluntary muscle contraction or muscle percussion.[21] They are due to independent, repetitive discharges of single muscle fibers. To be accepted as true myotonic discharges, the amplitude and frequency of the potentials must wax and wane, producing a characteristic divebomber or motorcycle sound in the audio display of the EMG. Complex repetitive discharges are a series of polyphasic or serrated action potentials that may begin spontaneously or after a needle movement; have uniform frequency, shape, and amplitude; and are abrupt in onset, cessation, or change in configuration.[21] The amplitude of CRDs ranges from 100 μV to 1 mV, and the frequency of discharge ranges from 5 to 100 Hz. Complex repetitive discharges are seen in a wide variety of myopathic and lower motor neuron disorders.[22-24] The description of the EMG bursts of activity described in the patient of Celesia et al[7] lacks mention of waxing and waning amplitude and frequency, and their article was published before the criteria for separating true myotonic discharges from CRDs were well established. We believe that the burst of activity in the case of Celesia and colleagues may have been CRDs. The evidence both in our case and in that of Celesia and colleagues indicates that the myopathy was restricted to the hypertrophic limb, although longer follow-up is needed to exclude a very asymmetric presentation of a more generalized myopathy.

Why a progressive myopathy should develop in a limb afflicted with monomelic hypertrophy is unclear. It is possible that at an early embryonic stage the cell(s) destined to give rise to the affected limb segregated a genetic abnormality, such as a chromosomal anomaly or a mutation, that was later responsible both for focal macrosomia and for an abnormality of skeletal muscle. There are as many possible causes for this myopathy as there are inherited disorders of muscle associated with hypertrophy, including Duchenne-type and Becker's muscular dystrophies (although both patients are female), myotonia congenita of Thomsen and of Becker,[25-30] and limb-girdle muscular dystrophy.[31]

Muscle hypertrophy has been reported rarely in association with lesions of nerve, including radicular lesions,[4-6] and with chronic spinal muscular atrophy.[32] Monomelic amyotrophy due to focal anterior horn cell degeneration is now a well-recognized condition,[33] but this has not been reported to be associated with muscle hypertrophy. The increased fiber density in the affected tibialis anterior muscle on single-fiber EMG in our case, together with increased jitter and blocking, suggested some neuronal involvement,[17] although the muscle biopsy findings and EMG indicated that the process was primarily a myopathy.

The various acquired forms of generalized muscle hypertrophy also need to be considered as causes for this monomelic myopathy. Such conditions include de Lange's syndrome,[34] hypothyroid myopathy,[35,36] and amyloid myopathy.[37,38] Hypertrophia musculorum vera is not a specific disease entity but rather is a syndrome of diffuse muscular hypertrophy of multiple causation.[1] Focal nodular myositis[39] may cause focal muscle hypertrophy, and monomelic myositis has been described.[40-42] However, all of these acquired causes of muscle hypertrophy appear unlikely to be relevant in these two cases of congenital monomelic hypertrophy with myopathy in view of the macrosomia and the muscle biopsy changes. It appears, therefore, that the case of Celesia et al[7] and our case represent similar but slightly different diseases of muscle occurring in a limb affected by congenital monomelic hypertrophy. The understanding of the basis of these muscle degenerations may come from advances in the molecular genetics of muscle disease.

We are grateful to Robert Greenwood, MD, for referring this patient and to the Department of Pathology of Duke University, Durham, NC, for access to slides of the pathologic material in this case.

References

1. Walton J, Gardner-Medwin D. The muscular dystrophies. In: Walton J, ed. *Disorders of Voluntary Muscle.* 5th ed. New York, NY: Churchill-Livingstone Inc; 1988:519.

2. Gowers WR. *Pseudohypertrophic Muscular Paralysis.* New York, NY: Churchill-Livingstone Inc; 1879.

3. Bruck F. Ueber einen Fall von congenitaler Makroglossie, combinirt mit allgemeiner wahrer Muskelhypertrophie und Idiotie. *Dtsch Med*

Wochenschr. 1889;15:229-257.

4. Mielke U, Ricker K, Emser W, Boxler K. Unilateral calf enlargement following S1 radiculopathy. *Muscle Nerve.* 1982;5:434-438.

5. Montagna P, Martinelli P, Rasi F, Cirignotta F, Govoni E, Lugaresi E. Muscular hypertrophy after chronic radiculopathy. *Arch Neurol.* 1984;41:397-398.

6. McComas JA. *Neuromuscular Function and Disorders.* Stoneham, Mass: Butterworth Publishers Inc; 1977.

7. Celesia GG, Andermann F, Wiglesworth FW. Monomelic myopathy: congenital hypertrophic myotonic myopathy limited to one extremity. *Arch Neurol.* 1967;17:69-77.

8. Del Torto P. Sopra due casi di macrosomia parziale congenita. *Arch Ortop.* 1925;41:470-472.

9. Ruggeri L, Bartolini G. Manifestazioni ipertrofiche monomelichenel quadro dell neurofibromatosi di Recklinghausen. *Minerva Ortop.* 1961;12:773-782.

10. Gerloczy F, Letenyei C, Szenasy L, et al. Contribution a l'étude de l'hemihypertrophie (à propos de 10 nouveaux cas d'hemihypertrophie vraie). *Acta Paediatr Acad Sci Hung.* 1963;4:159-183.

11. Zellweger H, Bell WE. Congenital muscular hypertrophy. *Neurology.* 1959;9:160-166.

12. Berger O. Zur Aetiologie und Pathologie der sogenannten Muskelhypertrophie. *Dtsch Arch Klin Med.* 1872;9:363-396.

13. Kalischer S. Ueber angeborenen Muskelkrampf und Hypertrophie an der linken oberen Extremitat. *Zbl Ges Neurol Psychiatr.* 1898;17:107-115.

14. Fraumeni JF, Geiser CF, Manning MD. Wilms' tumor and congenital hemihypertrophy. *Pediatrics.* 1967;40:886-899.

15. Labrune B, Labrune M. Hemi-hypertrophies corporelles chez l'enfant. *Pediatrie.* 1974;24:4821.

16. Galamero PC, Mussa GC. Contributo allo studio delle ipertrofie congenite: illustrazione di un caso di emiipertrofia e di due casi di monoipertrofia. *Minerva Pediatr.* 1962;14:344-355.

17. Stalberg E, Trontelj J. *Single Fibre Electromyography.* The Old Woking, Surrey, England: Mirvalle Press Ltd;1979.

18. Horton BT. Hemihypertrophy of extremities associated with congenital arteriovenous fistula. *JAMA.* 1932;98:373-379.

19. Stonjanov P. Klippel-Trenaunay syndrome. *Lancet.* 1962;2:1331-1332.

20. Lhermitte J. Hypertrophie des muscles de la jambe consecutive à une lesion du nerve sciatique par balle. *Rev Neurol.* 1918;33:529-530.

21. American Association of Electromyography and Electrodiagnosis. AAEE glossary of terms in clinical electromyography. *Muscle Nerve.* 1987;10(suppl):G1-G60.

22. Kimura J. *Electrodiagnosis in Diseases of Nerve and Muscle: Principles and Practice.* Philadelphia, Pa: FA Davis Co Publishers; 1984.

23. Emeryk B, Hausmanowa-Petrusewicz I, Nowak T. Spontaneous volleys of bizarre high frequency potentials (b.h.f.p.) in neuromuscular diseases, I: occurrence of spontaneous volleys of b.h.f.p. in neuromuscular diseases. *Electromyogr Clin Neurophysiol.* 1974;14:303-312.

24. Emeryk B, Hausmanowa-Petrusewicz I, Nowak T. Spontaneous volleys of bizarre high frequency potentials (b.h.f.p.) in neuromuscular diseases, II: an analysis of the morphology of spontaneous volleys of b.h.f.p. in neuromuscular diseases. *Electromyogr Clin Neurophysiol.* 1974;14:339-354.

25. Auerbach L. Ein Fall von wahrer Muskelhypertrophie. *Virchows Arch A.* 1871;53:397-417.

26. Van Bogaert ML. Maladie de Thomsen unilaterale (presentation d'un malade). *J Neurol.* 1927;27:426-428.

27. Caughey JE, Myrianthopoulos NC. *Dystrophia Myotonica Related Disorders.* Springfield, Ill: Charles C Thomas Publisher; 1963.

28. Dodge PR, Gamstorp I, Byers RK, Russell P. Myotonic dystrophy in infancy and childhood. *Pediatrics.* 1965;35:3-19.

29. Pruzanski W. Variants of myotonic dystrophy in pre-adolescent life (the syndrome of myotonic dysembryoplasia). *Brain.* 1966;89:563-568.

30. Vanier TM. Dystrophia myotonica in childhood. *Br Med J.* 1960;2:1284-1288.

31. Bradley WG. The limb-girdle syndromes. In: Vinken P, Bruyn GW, eds. *Handbook of Clinical Neurology.* New York, NY: Elsevier Science Publishing Co Inc; 1979;40:433-469.

32. Gardner-Medwin D, Hudgson P, Walton JN. Benign spinal muscular atrophy arising in childhood and adolescence. *J Neurol Sci.* 1967;5:14-58.

33. Gourie-Devi M, Turuvekert G, Susaralak S. Monomelic myotrophy. *Arch Neurol.* 1984;41:388-394.

34. de Lange C. Congenital hypertrophy of muscles: extrapyramidal motor disturbances and mental deficiency. *AJDC.* 1934;48:243.

35. Kendall-Taylor P, Tumbull DM. Endocrine myopathies. *Br Med J.* 1983;287:705-708.

36. Swanson JW, Kelly JJ, McConahey WM. Neurological aspects of thyroid dysfunction. *Mayo Clin Proc.* 1981;56:504-512.

37. Whitaker JN, Hashimoto K, Quinones M. Skeletal muscle pseudohypertrophy in primary amyloidosis. *Neurology.* 1977;27:47-54.

38. Ringel SP, Claman HN. Amyloid-associated muscle pseudohypertrophy. *Arch Neurol.* 1982;39:413-417.

39. Cumming WJK, Weiser R, Teoh R, Hudgson P, Walton JN. Localised nodular myositis: a clinical and pathological variant of polymyositis. *Q J Med.* 1977;46:531-546.

40. Enzinger FM, Dulcey FP. Proliferative myositis: report of 13 cases. *Cancer.* 1967;20:2213-2223.

41. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: part 1. *Ann Neurol.* 1985;17:215-227.

42. Mastaglia FL, Ojeda VJ. Inflammatory myopathies: part 2. *Ann Neurol.* 1985;17:317-323.

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Fellowships

PAIN FELLOWSHIP. The Pain Service in the Department of Neurology at Memorial Sloan-Kettering Cancer Center is seeking a board-eligible/board-certified neurologist for a pain fellowship. This is a one- or two-year position that offers comprehensive training in pain evaluation and treatment, with a strong emphasis on cancer pain. Fellows will participate in clinical investigations of neuro-oncologic pain syndromes and the pharmacology of opioid analgesics. Laboratory research opportunities directed at the mechanisms of opiate action and the molecular pharmacology of opiate receptors are also available. Please contact: K.M. Foley, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

FELLOWSHIP in Cerebrovascular Disease: Fellowships in cerebrovascular disease are available in the Department of Neurology at the University of Iowa. Comprehensive clinical training in management of patients with stroke is complemented by opportunities for clinical or basic research. Fellows are active participants in patient care and collaborate in several on-going local and multi-center clinical research studies. Candidates should be board-eligible or -certified in neurology and be licensed to practice medicine in the United States. Please send inquiries to either Harold P. Adams, Jr., MD, or Jose Biller, MD, Division of Cerebrovascular Diseases, Department of Neurology, University of Iowa, Iowa City, IA 52242. Or call: (319) 356-4110. The University of Iowa is an affirmative action/equal opportunity employer. Women, minorities and handicapped are encouraged to apply.

Neuro-Ophthalmology Fellowship

The Departments of Ophthalmology and Neurology, University of Michigan. Position for one year period, July 7, 1992 to July 6, 1993. Trainee appointed as a lecturer with stipend and fringe benefits. Inquiries (before June 1, 1991) to: Jonathan D. Trobe, MD,

W K Kellogg Eye Center
1000 Wall Street, Ann Arbor, MI 48105
The University of Michigan
is an affirmative action employer.

GERIATRIC NEUROLOGY FELLOWSHIP. A two-year fellowship is available in geriatric neurology, beginning July 1, 1991. This VA-supported fellowship provides multi-disciplinary training in geriatric neurology with formal rotations on the 17-bed Geriatric Evaluation and Management Service at the Portland VA Medical Center. Fellows will also participate in clinical and research activities of the Alzheimer's Disease Center of Oregon and the Oregon Brain Aging Study at both the VA Medical Center and Oregon Health Sciences University. Emphasis will be placed on the design and implementation of independent research protocols. A broad range of research opportunities are available and include such topics a quantitative image analysis, the neuropharmacology of movement disorders, cerebrovascular disease in the elderly, and the neurology, neuropsychology and neuropathology of the very old. Applicants must be board-eligible or -certified in neurology. To apply, send CV and two letters of recommendation to: Jeffrey Kaye, MD, Director, Geriatric Neurology, Portland VA Medical Center, 3710 SW U.S. Veterans Hospital Road, P.O. Box 1034, Portland, OR 97207. Telephone: (503) 273-5171 or (503) 494-7772. The Department of Veterans Affairs and the Oregon Health Sciences University are equal opportunity employers.

THE DEPARTMENT OF NEUROLOGY, University of Louisville has an opening for Clinical Neurophysiology Fellowship for 1991-92. Candidate will have the options to combine EEG with EMG or evoked potentials or clinical polysomnography. Interested applicants should forward their curriculum vitae to: Vasudeva Iyer, MD, Department of Neurology, University of Louisville, Louisville, KY 40292. (502) 588-7981.

PLEASE NOTE—Address replies to box number ads as follows: Box number, ______, c/o AON, P.O. Box 1510, Clearwater, FL 34617.

Neuro-oncology Fellowships/ Instructorships July 1991 and 1992

The U.C., San Francisco Neuro-oncology Service offers unprecedented opportunities to participate in chemotherapy and radiation therapy trials of children and adults with brain tumors.

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Michael Prados, MD
Department of Neurological Surgery
Neuro-oncology Service, ACC841
UNIVERSITY OF CALIFORNIA SAN FRANCISCO
San Francisco, CA 94143-0372

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POSTDOCTORAL FELLOWSHIP IN NEUROBEHAVIOURAL RESEARCH

The Rotman Research Institute of Baycrest Centre for Geriatric Care in Toronto is offering a two-year Postdoctoral Fellowship, starting in the summer of 1991.

The Rotman Research Institute is dedicated to research into neurobehavioural changes which occur during aging, with a specific focus on memory and frontal lobe functions. Baycrest Centre for Geriatric Care is fully affiliated with the University of Toronto and provides a comprehensive range of inpatient and outpatient services to the elderly in behavioural neurology, geriatric medicine, psychiatry, psychology, speech pathology, and other therapeutic services.

A minimum of eighty percent of the positions will be devoted to research and related activities. The stipend is equivalent to the fellowship scales of the Medical Research Council of Canada, and includes an allowance for travel and other research expenses. The position is open to applicants with a PhD, MD, or equivalent degree. In accordance with Employment & Immigration Canada regulations, preference will be given to Canadian citizens and permanent residents of Canada.

Applicants should send a complete CV and arrange to have three letters of reference sent separately, by February 1, 1991, to:

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ROTMAN RESEARCH INSTITUTE
BAYCREST CENTRE
FOR GERIATRIC CARE
3560 BATHURST STREET
TORONTO, ONTARIO, M6A 2E1, CANADA
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Fellowships

NEUROLOGICAL REHABILITATION Fellowship: The Department of Neurology of the University of California at Los Angeles offers an ongoing one- and two-year fellowship for BE/BC neurologists in neurorehabilitation starting every July. Acute inpatient and outpatient training within the U.C.L.A. Comprehensive Rehabilitation Program also provides opportunities in basic and clinical research in mechanisms of cognitive and motor recovery. The Functional Assessment Lab offers biochemical studies of gait, balance and strength. The inpatient rehab unit at Daniel Freeman Memorial Hospital provides additional training. Send inquiries, CV. and letters of recommendation to: Bruce H. Dobkin, MD, Professor of Neurology, UCLA School of Medicine, 300 UCLA Medical Plaza, Suite B200, Los Angeles, CA 90024-6975.

Faculty Positions

THE DEPARTMENT OF NEUROLOGY at the University of Louisville, School of Medicine is seeking a faculty member for a full-time academic appointment. Applicant must be board-eligible in neurology and neurodiagnostics, preferably with a completed fellowship in neurophysiology and electrodiagnostic medicine. Must be committed to education both at the undergraduate and graduate levels. Contact: William H. Olson, MD, Chairman, Department of Neurology, University of Louisville, Louisville, KY 40292. (502) 588-7981. EO/AAE.

THE DEPARTMENT OF NEUROLOGY at the University of Missouri-Columbia School of Medicine is recruiting two pediatric neurologists. These faculty members will be responsible for teaching, patient care, and service with academic rank and compensation based upon training and experience. Candidates should have a strong clinical interest in pediatric neurology. Interested candidates should be board-certified or eligible for board-certification by the American Board of Psychiatry and Neurology. Please contact: William J. Crowley, Jr., MD, Professor and Chairman, UMC School of Medicine, Department of Neurology, M741 Health Sciences Center, Columbia, MO 65212. The University of Missouri-Columbia is an equal opportunity and affirmative action institution.

THE UNIVERSITY OF MISSISIPPI Medical Center Department of Neurology invites applications for position of assistant professor from board-certified individuals with strong research, clinical and teaching skills. Persons with expertise in neuro-oncology, vascular disease and epilepsy are especially being sought. Please submit a letter of intent, curriculum vitae, and the names of three referring physicians to: Dr. James J. Corbett, Chairman, Department of Neurology, The University of Mississippi Medical Center, Jackson, MS 39216-4505. The University of Mississippi is an equal opportunity employer, M/F/H/V.

ACADEMIC NEUROLOGIST with board-eligibility in EMG sought by the Department of Neurology at The George Washington University Medical Center in Washington, DC. This non-tenure track, junior faculty position includes teaching responsibilities, patient care and the opportunity to develop a neuromuscular/EMG program. A competitive salary and excellent fringe benefits are provided. The George Washington University is an equal opportunity employer. Applications will be accepted until the position is filled. Please send inquiries and curriculum vitae to: Helene A. Emsellem, MD, Acting Chairman, Department of Neurology, 2150 Pennsylvania Avenue, NW, Suite 7-407, Washington, DC 20037.

ACADEMIC NEUROLOGIST with board-eligibility in clinical neurophysiology is sought by The Department of Neurology of The George Washington University Medical Center in Washington, DC. This tenure track position offers an opportunity to be involved in an active academic EEG/Sleep Laboratory and includes teaching and patient care activities. A competitive salary and excellent fringe benefits are provided. The George Washington University is an equal opportunity employer. Applications will be accepted until the position is filled. Please send inquiries and curriculum vitae to: Helene A. Emsellem, MD, Acting Chairman, Department of Neurology, 2150 Pennsylvania Avenue, NW, Suite 7-407, Washington, DC 20037.

Faculty Positions

FULL-TIME ACADEMIC POSITION in small, but ambitious department of neurology in private medical school in southeastern Virginia. Candidate should be BC/BE in neurology and have special expertise and additional training in clinical neuromuscular disease and electrodiagnostic medicine suitable for certification by ABEM. Training in muscle biopsy/pathology is especially desirable. Contact: Thomas R. Pellegrino, MD, Professor and Chairman, Department of Neurology, 825 Fairfax Avenue, Norfolk, VA 23507. (804) 446-5940.

LOYOLA UNIVERSITY Chicago Stritch School of Medicine, Department of Neurology invites applications for two positions at the assistant professor level. Applicants should be board-eligible or -certified in neurology and have subspecialty expertise in either epilepsy, movement disorders, cerebrovascular or neuromuscular diseases. Preference will be given to candidates with clinical research interests. Send CV to: Gastone Celesia, MD, Chairman, Neurology Department, Loyola University Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola University Chicago is an equal opportunity/affirmative action employer.

FULL-TIME ACADEMIC POSITION available in small but ambitious department of neurology in private medical school in southeastern Virginia; should be BC/BE clinical neurologist with special expertise and fellowship training in clinical neurophysiology suitable for certification by ABCN. Interest and expertise in clinical research highly desirable. Available facilities include intraoperative EEG/EP, ambulatory cassette EEG, video EEG, EEG/EP mapping. Contact: Thomas R. Pellegrino, Professor and Chairman, Department of Neurology, Eastern Virginia Medical School, 825 Fairfax Avenue, Norfolk, VA 23507. (804) 446-5940.

Residencies

THE UNIVERSITY OF CHICAGO Neurology Department is offering a second year neurology residency position (PGY 3) beginning July 1991. For information contact: Richard P. Kraig, PhD, MD, Residency Director, Department of Neurology, University of Chicago Medical Center, 5841 South Maryland, BH - Box 425, Chicago, IL 60637. (312) 702-0151.

Practices Available

JULY 1991—PRACTICE. Outstanding opportunity. $200K net probable by end of first year. Fully equipped neurologic institute. Only the best need apply. Send CV at once: Southeastern Neuroscience Institute, Inc., 5143 University Boulevard, West, Suite 3, Jacksonville, FL 32216-5939. (904) 733-0707; FAX (904) 730-9173.

Practices Available

NEUROLOGY PRACTICES for sale—Two established neurology practices for sale in Los Angeles County. A highly profitable, general neurology practice established over ten years, located on the campus of a major medical center in Burbank, California; and a busy pediatric neurology practice in Hollywood, California affiliated with major teaching and community hospitals. Call: Alex Guttman, Principal, Arthur S. Shorr and Associates, Inc., Consultants to Health Care Providers: (818) 348-6632.

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Miscellaneous

SECOND DARTMOUTH International Conference on Epilepsy and The Corpus Callosum, Hanover, New Hampshire, August 13-17, 1991. Contact: Professor Alexander G. Reeves, Section of Neurology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756. FAX: (603) 646-8756. Telephone: (603) 646-7916.

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Spinal Cord and Disc
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Each participant will have an exam and critique session and observation of other sessions. Additional 25 minute sessions may be arranged for $70 and private sessions may be had for an extra $30.

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INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cere
dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended
reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms p
termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importa
adhering strictly to the prescribed dosage regimen, and of informing the physician of any c
condition in which it is not possible to take the drug orally as prescribed, eg, surgery, et

Patients should also be cautioned on the use of other drugs or alcoholic beverages witho
seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimiz
development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve o
dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin le
which phenytoin may affect. Serum level determinations for phenytoin are especially h
when possible drug interactions are suspected. The most commonly occurring drug intera
are listed below: 1. Drugs which may increase phenytoin serum levels include: acute al
intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disul
estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiaz
phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol a
reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calciu
which interfere with the absorption of phenytoin. Ingestion times of phenytoin and a
preparations containing calcium should be staggered in patients with low serum phenytoin
to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenoba
sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, va
acid, and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizu
susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phe
include: corticosteroids, coumarin anticoagu
digitoxin, doxycycline, estrogens, furosemide,
contraceptives, quinidine, rifampin, theophy
vitamin D.

Drug/Laboratory Test Interactions: Phenytoin
cause decreased serum levels of protein-bound i
(PBI). It may also produce lower than normal valu
dexamethasone or metyrapone tests. Phenytoi
cause increased serum levels of glucose, alkaline
phatase, and gamma glutamyl transpeptidase (
Carcinogenesis: See "Warnings" section for info
tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug bec
phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encoun
with phenytoin therapy are referable to this system and are usually dose-related. These in
nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizzi
insomnia, transient nervousness, motor twitchings, and headaches have also been observed.
have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tr
and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients rece
long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver dama
Integumentary System: Dermatological manifestations sometimes accompanied by fever
included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the
common; other types of dermatitis are seen more rarely. Other more serious forms which
be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Ste
Johnson syndrome, and toxic epidermal necrolysis (see Precautions).
Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been rep
in association with administration of phenytoin. These have included thrombocytopenia, le
penia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow
pression. While macrocytosis and megaloblastic anemia have occurred, these conditions us
respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, p
dolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).
Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gin
hyperplasia, hypertrichosis, and Peyronie's Disease.
Cardiovascular: Periarteritis nodosa.
Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, sympt
such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), syst
lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estim
to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other sign
tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may bec
comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels w
toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia a
mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL
as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As m
as 25 times the therapeutic dose has been taken to result in a serum concentration over
mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed
appropriate supportive measures employed. Hemodialysis can be considered since pheny
is not completely bound to plasma proteins. Total exchange transfusion has been used in
treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, shoul
borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G

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Revised July 1

PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950

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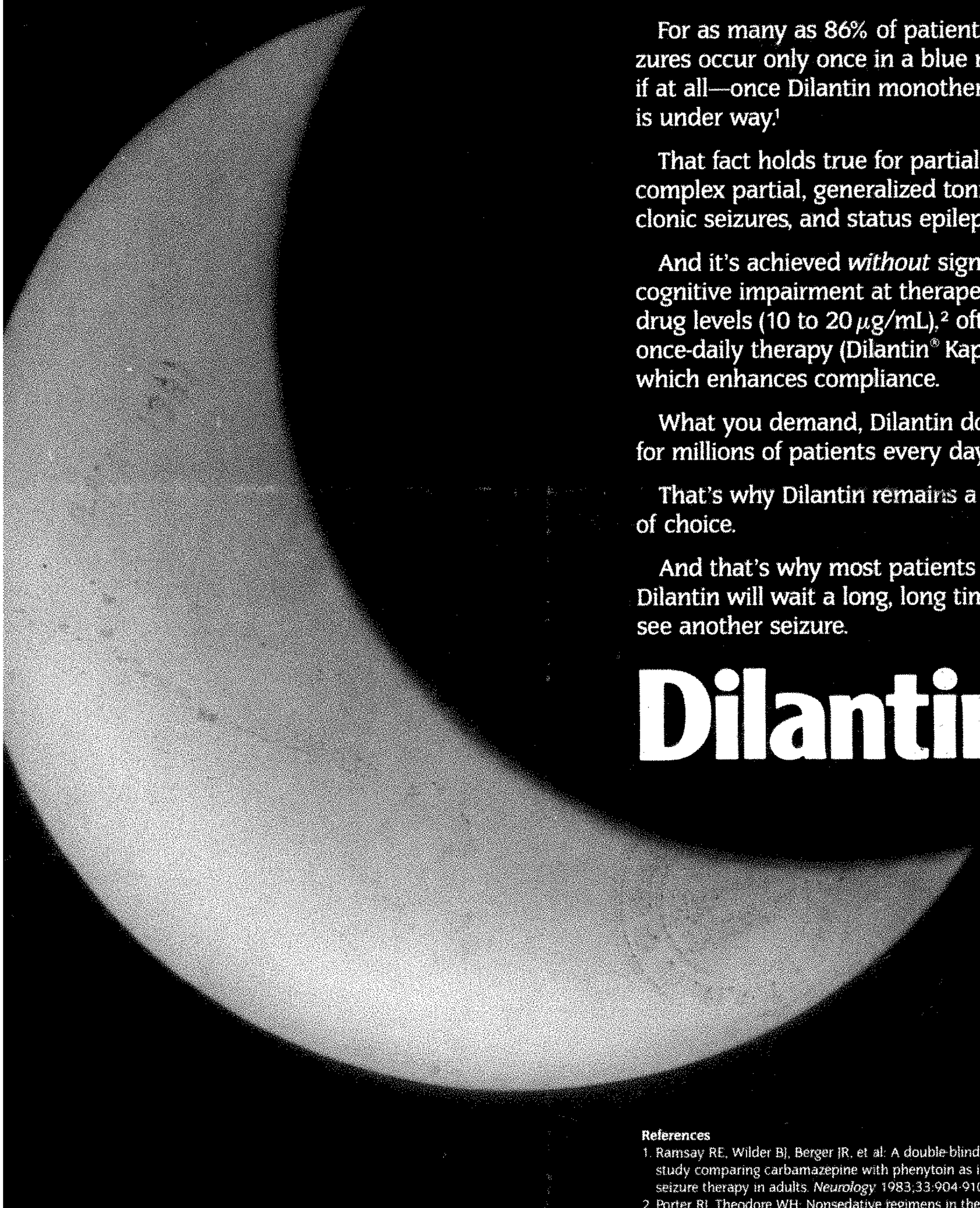

s rare as a seizure on ilantin® (extended phenytoin sodium capsules, USP) 100 mg

For as many as 86% of patients, seizures occur only once in a blue moon—if at all—once Dilantin monotherapy is under way.[1]

That fact holds true for partial, complex partial, generalized tonic-clonic seizures, and status epilepticus.

And it's achieved *without* significant cognitive impairment at therapeutic drug levels (10 to 20 μg/mL),[2] often *with* once-daily therapy (Dilantin® Kapseals®), which enhances compliance.

What you demand, Dilantin does—for millions of patients every day.

That's why Dilantin remains a drug of choice.

And that's why most patients on Dilantin will wait a long, long time to see another seizure.

Dilantin®

e in a blue moon" describes the phenomenon in which moon appears as a brilliant blue. Seen worldwide following volcanic eruption of Krakatoa in 1883, the blue moon occurs when atmospheric cloud droplets, each less than 5 μm in meter, form in abundance—an exceedingly rare event.[3]

References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976; 31:292-296.

Please see adjacent page for brief summary of prescribing information.

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90 Warner-Lambert Company

5 12/92

76

ARCHIVES OF Neurology

FEBRUARY 1991

Results of Surgery for Extratemporal Partial Epilepsy That Began in Childhood
J. Adler, G. Erba, K. R. Winston, K. Welch, C. T. Lombroso

P300 Brain Activity in Seizure Patients Preceding Temporal Lobectomy
C. A. Nelson, P. F. Collins, F. Torres

VCM

Cognition-Independent Neurologic Symptoms in Normal Aging and Probable Alzheimer's Disease
E. H. Franssen, B. Reisberg, A. Kluger, E. Sinaiko, C. Boja

Age at Onset of Alzheimer's Disease: Relation to Language Dysfunction
K. A. Bayles

Anatomic, Metabolic, Neuropsychological, and Molecular Genetic Studies of Three Pairs of Identical Twins Discordant for Dementia of the Alzheimer's Type
A. Kumar, M. B. Schapiro, C. L. Grady, M. F. Matocha, J. V. Haxby,
A. M. Moore, J. S. Luxenberg, P. H. St George-Hyslop,
C. D. Robinette, M. J. Ball, S. I. Rapoport

Volume 48, Number 2

American Medical Association
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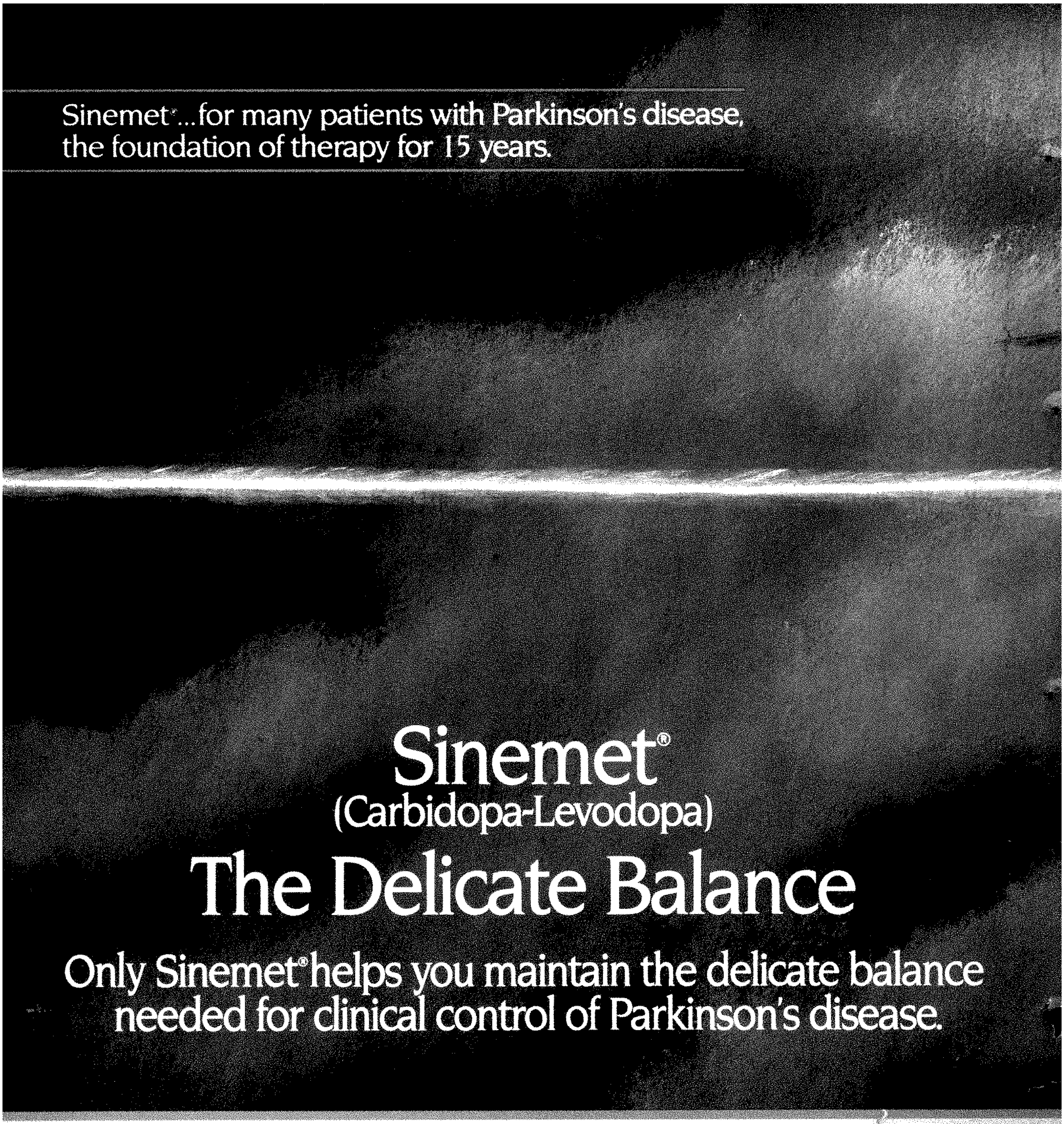
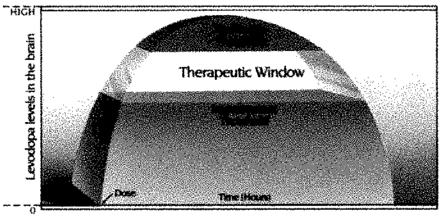


Sinemet®...for many patients with Parkinson's disease, the foundation of therapy for 15 years.

Sinemet®
(Carbidopa-Levodopa)
The Delicate Balance

Only Sinemet® helps you maintain the delicate balance needed for clinical control of Parkinson's disease.



Balancing Dopamine Replacement and Patient Response *Managing the symptoms of Parkinson's disease can be an ongoing balancing act, particularly as the disease progresses and the therapeutic window changes. By adjusting Sinemet® dosage strength and frequency according to patient needs, physicians can achieve the delicate balance needed between dopamine replacement and therapeutic response.*

The management of levodopa therapy in Parkinson's disease can be complex. It calls for a delicate balance between the relief of symptoms by the replacement of dopamine in the brain and the occurrence of side effects.

Dopamine replacement is the mainstay of therapy in Parkinson's disease. Only Sinemet® re-establishes dopamine levels in the brain.

But, too much or too little dopamine can affect the patient's quality of life. So dosage must be monitored and adjusted as the disease progresses, because the therapeuti window narrows over time.

Sinemet® provides you the flexibility needed to adjust dosage based on the individual patient's therapeutic window...by changing dosing frequency...dosage strength... or by changing the ratio between carbidopa and levodopa.

Nothing else helps you maintain the delicate balance needed to manage the signs and symptoms of Parkinson's disease like Sinemet®.

Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower doses and sooner with Sinemet® than with levodopa. The occurrence of dyskinesias may require dosage reduction. Please see a brief summary of prescribing information on the adjoining page.

Sinemet®
(Carbidopa-Levodopa)

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Pharmaceuticals

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For many patients with Parkinson's disease

Dosage Guidelines

***Individualized dosage—a key to clinical success with Sinemet*®**

- Begin when symptoms first interfere with normal function
- Adjust as necessary to help maintain relief of symptoms

1

For initial therapy...Start with:

SINEMET 25-100

containing 25 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

one tablet t.i.d.

If necessary, to control symptoms, dosage may be increased by one tablet every day or every other day until a dosage of eight tablets of Sinemet 25-100 a day is reached.

2

When it is evident that patients need more levodopa...Transfer to:

SINEMET 25-250

containing 25 mg carbidopa (anhydrous equivalent) and 250 mg levodopa

one tablet t.i.d.

If still more levodopa is necessary, dosage with Sinemet 25-250 may be increased by one-half to one tablet every day or every other day to a maximum of eight tablets a day.

3

When individualizing dosage...Titrate with:

SINEMET 10-100

containing 10 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

or SINEMET 25-100

or SINEMET 25-250

The optimum daily dosage of Sinemet must be determined by careful titration in each patient. Tablets of the three strengths may be given separately or combined as needed to provide the optimum daily dosage.

For patients transferred from levodopa

DISCONTINUE LEVODOPA AT LEAST 8 HOURS BEFORE STARTING SINEMET.

The starting dose for Sinemet should provide about 25 percent of previous levodopa requirements. (Patients receiving less than 1500 mg of levodopa a day should be started on one tablet of Sinemet 25-100 t.i.d. or q.i.d.)

Sinemet®

(Carbidopa-Levodopa)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System*: ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric*: confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal*: dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic*: weight gain or loss, edema. *Integumentary*: malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary*: urinary retention, urinary incontinence, dark urine, priapism. *Special Senses*: diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous*: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

Manufactured by:
MERCK SHARP & DOHME
DIV OF MERCK & CO., INC.,
WEST POINT, PA 19486, USA

FOR:

DU PONT

Du Pont Pharmaceuticals
E.I. duPont de Nemours & Co.
Wilmington, Delaware 19898

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(Carbidopa-Levodopa)

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CALENDAR 125

NEWS 126

BOOKS

Mutism: Studies in Disorders of Communication 129
Yvan Lebrun, Reviewed by Victor W. Henderson, MD, Los Angeles, Calif

Trends in Neuroimmunology 129
M. G. Marrosu; C. Cianchetti; B. Tavolato, (eds),
Reviewed by David H. Mattson, MD, PhD, Rochester, NY

Neurologic Clinics 129
William H. Theodore, (ed), Reviewed by Roger Kurlan, MD, Rochester, NY

Vascular Brain Stem Diseases 130
B. Hofferberth; G. G. Brune; G. Sitzer; H.-D.Weger, (eds),
Reviewed by José Biller, MD, Betsy B. Love, MD, Iowa City, Iowa

Computational Neuroscience 130
Eric L. Schwartz, (ed), Reviewed by James L. Ringo, PhD, Rochester, NY

LETTERS TO THE EDITOR

Seizures Following Carotid Endarterectomy 131
MAJ Stuart E. Sinoff, MC, USA, Washington, DC

In Reply
Karl Kieburtz, MD, MPH, Richard T. Moxley III, MD, Rochester, NY

Convergence Nystagmus Associated With Arnold-Chiari Malformation 131
Rosolino M. Camarda, MD; Domenico Raimondo, MD;
Marisa Rosetti, MD, Palermo, Italy

In Reply
Brian Kendall, FRCP; S. S. Mossman, MD;
A. M. Bronstein, MD;
M. A. Gresty, PhD; P. Rudge, FRCP, London, England

Continued on page 123.

HEADACHE DESCRIBED

"Headache"—a personal interpretation of headache pain by John Crowley, a headache patient.

HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL WITH CODEINE CIII CAPSULES

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

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FWC-0790-01

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming]; butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Placebo (N = 377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

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[NOVEMBER 1, 1990 FWC-Z26]

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ARCHIVES

ORIGINAL CONTRIBUTIONS

Results of Surgery for Extratemporal Partial Epilepsy That Began in Childhood 133
John Adler, MD, Stanford, Calif; Giuseppe Erba, MD, Rochester, NY;
Ken R. Winston, MD, Denver, Colo; Keasley Welch, MD,
Cesare T. Lombroso, MD, PhD, Boston, Mass

P300 Brain Activity in Seizure Patients Preceding Temporal Lobectomy 141
Charles A. Nelson, PhD; Paul F. Collins;
Fernando Torres, MD, Minneapolis, Minn

Cognition-Independent Neurologic Symptoms in Normal Aging and Probable Alzheimer's Disease 148
Emile H. Franssen, MD; Barry Reisberg, MD; Alan Kluger, PhD;
Elia Sinaiko, PhD; Conrado Boja, MD, New York, NY

Age at Onset of Alzheimer's Disease: Relation to Language Dysfunction 155
Kathryn A. Bayles, PhD, Tucson, Ariz

Anatomic, Metabolic, Neuropsychological, and Molecular Genetic Studies of Three Pairs of Identical Twins Discordant for Dementia of the Alzheimer's Type 160
Anand Kumar, MD; Mark B. Schapiro, MD; Cheryl L. Grady, PhD;
Martha F. Matocha, PhD; James V. Haxby, PhD; Angela M. Moore, MS;
Jay S. Luxenberg, MD, Bethesda, Md;
Peter H. St George-Hyslop, PhD, Boston, Mass;
Charles D. Robinette, PhD, Washington, DC;
Melvyn J. Ball, MD, London, Ontario;
Stanley I. Rapoport, MD, Bethesda, Md

The Distribution of Cerebral Muscarinic Acetylcholine Receptors In Vivo in Patients With Dementia: A Controlled Study With ^{123}IQNB and Single Photon Emission Computed Tomography 169
Daniel R. Weinberger, MD; Raymond Gibson, PhD; Richard Coppola, DSc;
Douglas W. Jones, PhD; Susan Molchan, MD; Trey Sunderland, MD;
Karen Faith Berman, MD; Richard C. Reba, MD, Washington, DC

Widespread Functional Effects of Discrete Thalamic Infarction 178
Brigitte Szelies, MD; Kare Herholz, MD; Gunther Pawlik, MD;
Hans Karbe, MD; Ira Hebold, MD;
Wolf-Dieter Heiss, MD, Cologne, Federal Republic of Germany

Spectral Analysis of Heart Rate in Diabetic Autonomic Neuropathy: A Comparison With Standard Tests of Autonomic Function 185
Roy Freeman, MD; J. Philip Saul, MD; Mark S. Roberts, MD, MPP;
Ronald D. Berger, MD, PhD; Christopher Broadbridge;
Richard J. Cohen, MD, PhD, Boston, Mass

Treatment of Multiple Sclerosis With Hyperbaric Oxygen: Results of a National Registry 195
Eric P. Kindwall, MD, Milwaukee, Wis;
Michael P. McQuillen, MD, Lexington, Ky;
Bhupendra O. Khatri, MD, Milwaukee, Wis;
Harvey W. Gruchow, PhD, Greensboro, NC;
Marilyn L. Kindwall, MS, Milwaukee, Wis

Continued on page 124.

ARCHIVES

Alterations in Brain Phosphate Metabolite Concentrations in Patients With Human Immunodeficiency Virus Infection 203
Raymond F. Deicken, MD; Bruno Hubesch, PhD; Peter C. Jensen, MD; Dominique Sappey-Marinier, PhD; Pamela Krell, PhD; Amy Wisniewski, PhD; Douglas Vanderburg, MD; Reginald Parks, MPH; George Fein, PhD; Michael W. Weiner, MD, San Francisco, Calif

The Effect of Sleep on the Dyskinetic Movements of Parkinson's Disease, Gilles de la Tourette Syndrome, Huntington's Disease, and Torsion Dystonia 210
David R. Fish, MD; Diane Sawyers; Philip J. Allen, MSc; Jeffrey D. Blackie, FRACP; Andrew J. Lees, FRCP; C. David Marsden, FRS, London, England

Intravenous Immunoglobulin Treatment in Patients With Chronic Inflammatory Demyelinating Polyneuropathy: Clinical and Laboratory Characteristics Associated With Improvement 217
P. A. van Doorn, MD, M. Vermeulen, MD, Rotterdam, the Netherlands; A. Brand, MD, Leiden, the Netherlands; P. G. H. Mulder, PhD, H. F. M. Busch, MD, the Netherlands

Posttraumatic Torticollis 221
Daniel D. Truong, MD, Irvine, Calif; Richard Dubinsky, MD, Kansas City, Kan; Neal Hermanowicz, MD, Ann Arbor, Mich; Walter L. Olson, MD, Maumee, Ohio; Bruce Silverman, DO, Detroit, Mich; William C. Koller, MD, PhD, Kansas City, Kan

CONSENSUS IN NEUROLOGY

Chemotherapy for Oligodendroglioma: Progress Report 225
J. Gregory Cairncross, MD, David R. Macdonald, MD, London, Ontario

Anaplastic Oligodendrogliomas 227
Terrence L. Cascino, MD, Rochester, Minn

Are Anaplastic Oligodendrogliomas Chemosensitive? 227
Vladimir Hachinski, MD, DSc (MED), London, Ontario

HISTORY OF NEUROLOGY

An Early Description of Slowly Progressive Aphasia 228
Claudio Luzzatti, MD, Klaus Poeck, MD, Aachen, Federal Republic of Germany

OBSERVATIONS

Anterior Femoral Cutaneous Nerve Injury Following Femoral Artery Reconstructive Surgery 230
Jerry M. Belsh, MD, New Brunswick, NJ

Frontal Impairment and Hypoperfusion in Neuroacanthocytosis 232
Florence Delecluse, MD; Jeanine Deleval, MS; Jean-Marie Gérard, MD; Alex Michotte, MD; Diederik Zegers de Beyl, MD, Brussels, Belgium

REGULAR DEPARTMENTS

Index to Advertising 128

Classified Advertising 237

Instructions for Authors —See January 1991 issue, p 14

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From refill to refill… which carbamazepine will your patient get next?

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the following page, especially the boxed warning.

CIBA–GEIGY

Prevent substitution when you prescribe Tegretol

Sign each prescription on the line that prevents substitution, or add the phrase required in your state to prevent substitution:

☐ Dispense As Written
☐ No Substitution
☐ Do Not Substitute
☐ Brand Necessary
☐ No Drug Product Selection
☐ May Not Substitute
☐ Medically Necessary

For your Medicaid patients…

To prevent substitution of TEGRETOL for your Medicaid patients, be sure to add the phrase "Brand Medically Necessary" on each prescription.

Tegretol®
carbamazepine USP

200-mg scored tablets
100-mg chewable tablets

…because there's no substitute for experience.

Tegretol® carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink **Tablets of 200 mg—pink**

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

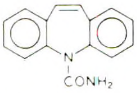
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz [b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes: Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD 50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression: Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE).

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE).

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit 12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture.

Dispense in tight container (USP).

Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles.

Printed in U.S.A. C90-34 (Rev. 6/90)

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Ardsley, New York 10502

Calendar

CALENDAR OF MEETINGS

1991		
Feb	2-3	Sixth Annual Neuroradiology Review Course, Hyatt Regency, Bethesda, Md. Contact Wendy S. Baker, Course Coordinator, Armed Forces Institute of Pathology, Washington, DC 20306-6000; (202) 576-2162.
	2-9	Second Annual Clinical Magnetic Resonance Imaging Meeting, Marriott's Mark Resort, Vail, Colo. Contact Program Coordinator, Department of Radiology, Program Committee, Box 17241, Tampa, FL 33682-7241; (813) 873-2090 or (800) 338-5901.
	8-10	"Clinical Neurology for Psychiatrists," Bahia Mar Resort, Ft Lauderdale, Fla. Contact Office of Continuing Medical Education, Albert Einstein College of Medicine / Montefiore Medical Center, 111 E 210th St, Bronx, NY 10461; (212) 920-6676.
	14-16	Annual Meeting of the Western Electroencephalographic Society, Portland Ore. Contact Bonnie Becker, Executive Secretary, Good Samaritan Hospital, Suite 400, 1040 NW 22nd Ave, Portland, OR 97210; (503) 229-7721.
	15-17	Sixth Meeting of The International Study Group of the Pharmacology of Memory Disorders Associated with Aging, Zurich, Switzerland. Contact Professor Richard J. Wurtman, Bldg E25-604, Whitaker College, Massachusetts Institute of Technology, Cambridge, MA 02139.
	15-17	The 24th Annual Recent Advances in Neurology, San Francisco, Calif. Contact Extended Programs in Medical Education, University of California, Room C-124, San Francisco, CA 94143-0742; (415) 476-4251.
	18-20	Fifth International Symposium on Intracranial Hemodynamics: Transcranial Doppler and Cerebral Blood Flow and Other Modalities, Hyatt Regency Embarcadero Center, San Francisco, Calif. Contact Conference Coordinator, Institute of Applied Physiology and Medicine, 701 16th Ave, Seattle, WA 98122; (206) 442-7330.
	20-23	"The Practicing Physician's Approach to the Difficult Headache Patient," Wyndham Hotel, Palm Springs, Calif. Contact Ms Idell Applebaum, Diamond Headache Clinic Research and Educational Foundation, 5252 N Western Ave, Chicago, IL 60625; (312) 878-5558.
	22-24	"Clinical Neurology for Psychiatrists," Fisherman's Wharf Holiday Inn, San Francisco, Calif. Contact Office of Continuing Medical Education, Albert Einstein College of Medicine / Montefiore Medical Center, 111 E 210th St, Bronx, NY 10461; (212) 920-6676.
March	7-9	"Recent Advances in Geriatric Medicine, New Treatment Options for Old Problems," The Pan Pacific Hotel, San Diego, Calif. Contact Cass Jones, Professional Conference Management Inc, 7916 Convoy Ct, San Diego, CA 92111; (619) 565-9921.
	14-16	"Brain Chemistry and Behavior: Advances in Positron Emission Tomography and Single Photon Emission Tomography Imaging," Baltimore, Md. Contact Patty Campbell, Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-3839.
	16-20	Fifth Annual Magnetic Resonance Imaging Conference, Marriott's Camelback Inn, Scottsdale, Ariz. Contact Kevin King, Education Coordinator, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 W Thomas Rd, Phoenix, AZ 85013; (602) 285-3956.
	17-21	The Eighth Conference of the Southeast European Society for Neurology and Psychiatry, Jerusalem, Israel. Contact Shaul Feldman, MD, PO Box 50006, Tel Aviv 61500, Israel.
	17-23	24th Latin American Congress of Neurosurgery, Miami, Fla. Contact Sergio Gonzalez-Arias, MD, 8950 N Kendall Dr, Suite 406, Miami, FL 33176; (305) 271-6159.
	18-20	"Spectrum of Developmental Disabilities: Cerebral Palsy: Issues of Early Detection and Intervention," The Johns Hopkins Medical Institutions, Baltimore, Md. Contact Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Bldg, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-2959.
	21-33	"Recent Advances in Neurology and Neurosurgery," Scottsdale, Ariz. Contact Toby A. Jardine, Manager, Administration, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix, AZ 85013; (602) 285-3178.
	23-24	Cervical and Lumbar Spine: Start of the Art '91, Hyatt Regency Embarcadero, San Francisco, Calif. Contact the San Francisco Spine Institute, 1850 Sullivan Ave, Suite 140, Daly City, CA 94015; (415) 991-6761.
April	10-11	The Second Annual Postgraduate Electromyography Review Course, Iowa City, Iowa. Contact Deborah L. Hatz, Program Coordinator, University of Iowa College of Medicine, Iowa City, IA 52242; (319) 335-8598.
	21-27	43rd Annual Meeting of the American Academy of Neurology, Hynes Convention Center, Boston, Mass. Contact American Academy of Neurology, 2221 University Ave SE, Suite 335, Minneapolis, MN 55414; (612) 623-8115.
	22	The Annual Meeting of the World Federation of Neurology Research Group on Neuroepidemiology, Boston, Mass. Contact Gustavo C. Román, Chief, Neuroepidemiology Branch, Federal Building, Room 714, 7550 Wisconsin Ave, National Institutes of Health, Bethesda, MD 20892; (301) 496-1714.
	29-May 5	Advances in Internal Medicine, The Towsley Center, Ann Arbor, Mich. Contact Julie Jacobs, Office of Continuing Medical Education, G-1100 Towsley Center, Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.
May	7-10	Ecuadoran Society of Neurology, Quito, Ecuador. Contact Ecuadoran Society of Neurology, PO Box 2821, Quito, Ecuador.
	27-29	New Frontiers on Acute Ischemic Stroke-An Update, Rome, Italy. Contact Stroke Secretariat, Via Bertolini, 26/B, 00197 Rome, Italy.
	30-June 1	International Conference on Stroke, Geneva, Switzerland. Contact N. M. Bornstein, MD, International Conference on Stroke, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211 Geneva, Switzerland.

News

American Board of Psychiatry and Neurology Inc.—The following individuals were certified in neurology at the examination held in March 1990:

Agrawal, Rakesh
Albers, Gregory William
Amos, Edwin Curtis
Bahamon-Dussan, Juan Ernesto
Bajwa, Ahsan Kalim
Bayne, Lydia
Becker, Philip Scott
Bowen, James Duane
Briley, Dennis Patrick
Call, Gregory K.
Callaghan, Maureen Ann
Carlson, Scott Eric
Chabay, Cynthia Lynn
Charnock, Edwin Howard
Cimera, James Lewis
Collins, Stephen Douglas
Culberson, Charles Gregory
Danesh, Mitchell Martin
Diringer, Michael Neil
Edmondson, Everton Anthony
Edmundson, Herbert Paine, Jr
Fieman, Sherry Lynn
Fleishman, Jerold Howard
Ford, Corey Charles
Frecker, David George
Geraghty, John Joseph III
Graham, Richard Alton
Graham, Steven Hunt
Helman, Dale Avry
Henning, William Eugene
Himel, Timothy Farrar
Holland, Marie Tulou
Hope, William Grant
Hosey, Jonathan P.
Johnston, James Christopher
Kahkeshani, Saeed
Kane, Jerome Marc
Kanter, Merrill Carolyn
Kershaw, Paul Russell
Kimpel, Thomas Guy
Kitt, Donald Conrad
Klingman, Jeffrey Gilbert
Licht, Harvey Jay
Little, James Hart
Lytton, William Winzer
Mao, Chi-Chen
Marra, Christina
Martin, Alan William
Massa, Stephen Mark
Mechtler, Laszlo Lipot
Mitchell, Thomas Alexander
Mody, Cyrus Khushroo
Mucke, Lennart
Murphy, Lawrence Cullum
Noebels, Jeffrey Lloyd
Noland, William Horace
Pulst, Stefan Matthias
Ribaudo, John Joseph
Ricalde, Orlando Arthur
River, Mary Elizabeth
Sanchez, Ramon Marcos
Scharre, Douglas W.
Schulz, Paul Ernest
Singh, Parduman
Sinoff, Stuart Evan
Spellman, Edward Lewis
Strassberg, Mark Howard
Tapscott, Stephen Justice
Townsend, John Barratt III
Vickrey, Barbara Grace
Vickroy, Joseph Walter, Jr
Welborn, Mark Gregory
Wheelock, Vicki Lynn
Wong, Bowen Yee
Yamut, Bassem Ibrahim

The following individuals were certified in neurology with special qualifications in child neurology:

Atkinson, Sid W.
Cohen, Bruce Howard
Crawford, Thomas Owen
Famiglio, Linda Marie
Gonzalez, Evelyn
Gowrinathan, Rani N.
Huang-Santos, Nancy T.
MacDonald, Gregory Paul
Makari, George S. H.
Maria, Bernard Lee
Marks, Warren Alan
Miller, Bradford Russell
Miller, Christopher Alan
Morales, Augusto
Morgan, Harley Bascom
Oliver, Young Pinckney
Smith, Mary Elizabeth
Virdi, Balbir Singh
White, Larry Eugene
Wical, Beverly Smith
Yamada, Kelvin Akira

American Board of Psychiatry and Neurology Inc.—The following individuals were certified in neurology at the examination held in June 1990:

Adams, Charles Robert
Amaraneni, Prasunamba G.
Anderson, Britt
Anstandig, Jack
Applegate, Clara Nancy
Armon, Carmel
Asconape, Jorge Juan
Baser, Susan Mary
Benarroch, Eduardo Elias
Benjamin, Debra A.
Bennett, David Alan
Bertoldi, Roger Victor
Carmickle, Lynn JoAnne
Carpenter, David Adams
Carpenter, Don Elton
Case, James Lawrence
de Alvare, Leopolde Angel
Dobmeyer, Susan Matilda
Enos, Bruce Edward
Epperson, Larry Wayne
Forchetti, Concetta Maria
Frere, Robert Carroll
Funkey, Richard Ivison
Gaffney, James Shannon
Gilder, Beverly Faye
Gitt, Jeffrey Scott
Goldman, Linda C.
Gomez, Camilo Ramiro
Gomez, Christopher Manuel
Graeber, Michael Coleman
Grosmann, Carla Margaret
Gupta, Vipin Kumar
Hanley, Daniel Francis
Hannam, John Michael
Harrison, Madaline Burr
Herron, Timothy
Homer, Daniel
Hudgens, Kyle Randall
Ibrahim, Waseem Nicola
Jagiella, Waclav M.
Janicki, Mark Joseph
Johnson, Rodney James
Jones, Robert Walter, Jr
Kanter, Roy Alan
Khabbazeh, Zuka Arabi
Knox, Craig Alan
Kundu, Subroto
Kuzniecky, Ruben Itamar
Kwentus, Joseph Allen
Lapham, Craig Allen
Leung, Patrick Kwok-Him
Lynch, James Edward
Mandell, Howard
McCahill, Kathleen Susan
Miles, Michael Francis
Minette, Susan Elaine
Mitchell, Galen Wesley
Moen, Margaret L.
Munschauer, Frederick E. III
Nadis, Susan Marsha
Nance, Martha Anne
Ortega, Steven Arthur
Pauxtis, Gregory F.
Pearlman, Robert Lawrence
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Puente, Michael Albert
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Ragland, James Balasundaram
Sahota, Pradeep K.
Scheyer, Richard David
Schreiber, Steven Scott
Shankle, William Rodman
Sharma, Khema Ram
Shipley, Winston Dean
Siegel, David Randolph
Snyder, Abraham Zvi
Srivastava, Madhav Kumar
Sullivan, Lawrence Patrick
Sund, Sheila Lynn
Sundell, Robert Raymond
Susskind, Cynthia Gaye
Taboas, Rafael A., Jr
Tempel, Lee W.
Thornton, Charles Allan
Trobiani, Steven
Undesser, Eric Karl
Venkatesh, Ram
Walk, David
Williams, Douglas Paul
Wilson, Elaine Jones
Wolfe, Irving Larry
Yerby, Mark S.

When the world turns upside down...

Transderm Scōp is the better choice for motion sickness prevention

- more effective than 25 mg meclizine and Dramamine®[1,2]
- better compliance because transdermal delivery is more convenient

Transderm Scōp®
scopolamine
programmed delivery
0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

CIBA

Transderm Scōp®

scopolamine
(formerly Transderm-V)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE
Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS
Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS
Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS
General
Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients
Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions
Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility
No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C
Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use
Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS
The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE
Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION
Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION
Federal law prohibits dispensing without prescription.

Dist. by:
CIBA Consumer Pharmaceuticals
Div. of CIBA-GEIGY Corp.
Summit, NJ 07901

C88-5 (Rev. 2/88)

CIBA

References:
1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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American Academy of Clinical Neurophysiology 202
The American Neurological Association 191-191
Berlex Imaging 192A-B, 193-194
Ciba Pharmaceutical Company 127-128, 215-216
Webb Dordick 216
Downstate Headache Center 202
Dupont Pharmaceuticals .... Cover 2-118
Geigy Pharmaceuticals ... 124A-B, 224A-B
Eli Lilly & Company 132A-D
Miles Pharmaceuticals 183-184
Neurofibromatosis Foundation 216
Osler Institute 224
Parke-Davis .... 176A-B, 177, Cover 3-Cover 4
Sandoz Pharmaceuticals . 120-122, 200-202
Wyeth-Ayerst Laboratories 235-236

While every precaution is taken to ensure accuracy, we cannot guarantee against the possibility of an occasional change or omission in the preparation of this index.

Books

Mutism: Studies in Disorders of Communication, by Yvan Lebrun, 124 pp, $29, London, England, Whurr Publishers, 1990.

Lebrun's short monograph offers a readable overview of mutism in all of its aspects. The text presents a wide-ranging pastiche of sundry "condition[s] in which there is no, or very little, oral-verbal expression, whilst comprehension . . . is normal or at least at a considerably higher level than oral-verbal output" (p 1). Organized into a short chapter on the psychology of silence and two longer chapters on functional mutism and organic mutism, the book is significant more for its breadth than for its depth. The text is amply referenced and has a useful subject and author index.

Topics, almost dazzling in their variety, range from akinetic mutism to aphemia, from esophageal speech to speech apraxia, from monastic silence to the family dynamics of children who maintain silence at school, from mutism after cerebral commissurotomy to muteness of the famous "wild child" of Aveyron. Lebrun's general approach is to provide vignettes illustrating each subject under discussion. Here the book is at its lucid best. Vignettes include not only generous summaries of case reports from the clinical literature but also illuminating examples from art, classic and modern literature, mythology, the Bible, and anthropology. Even etymology and slang expression find their way into Lebrun's eclectic treatise.

Mutism is more descriptive than explanatory, and some neurologists will look askance at the treatment of certain material. How, for example, are eating, toileting, copulating, and speaking—the four "primary modes of interaction with the environment" (p 45)—alike? Each of these, according to Lebrun in a discussion of functional mutism dynamics, "help[s] the individual outgrow an initial state of egocentrism and adapt to social life" (p 46). And what is a biologically oriented neuroscientist to conclude when words are metaphorically likened to sperm? Cursory explanations of organic causes of mutism are also disappointing in their pathophysiologic and anatomic simplicity.

Is *Mutism* an essential reference for the neurologist's personal library? I think not. However, *Mutism* is an enjoyable survey that provides a broad, well-referenced introduction to multifaceted aspects of speechlessness; it is on this basis that I recommend the book.

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Trends in Neuroimmunology, edited by M. G. Marrosu, C. Cianchetti, and B. Tavolato, 169 pp, $50, New York, NY: Plenum Press, 1990.

This book represents the proceedings of the International Symposium on Trends in Neuroimmunology, Cagliari, Italy, in 1988. Based on this book, the symposium was excellent and would have been well worth attending. The authors of chapters are a distinguished international group of neuroimmunologists, mostly from Italy and other parts of Europe.

The book is organized into chapters on four broad areas representing current aspects of intense interest in neuroimmunology—humoral immunity, cellular immunity, immune functions of glia, and central nervous system immune diseases. Chapters describing work in human and animal systems are intermingled in a mutually reinforcing and provocative manner. Most of the chapters are original research reports, but two are review articles.

Several of the chapters describing original research reports are excellent, state-of-the-art accounts, some of which have subsequently either partially or completely appeared in print in refereed journals. These include chapters on antioligodendrocyte autoreactive T cells, human fetal brain cultures, and immunologic parameters and therapies in an impressive number of patients with subacute sclerosing panencephalitis. The chapter describing a negative search for human T-cell lymphotropic virus type I in patients with multiple sclerosis using polymerase chain reaction techniques is excellent, provides guidelines for others doing similar work, and has not appeared in any form elsewhere. Other chapters, however, on cerebrospinal fluid findings in patients infected with human immunodeficiency virus type 1 or in patients with MS discuss old techniques and confirm well-established concepts in Italian populations, or rework topics such as central nervous system IgG synthesis or B-cell responses in multiple sclerosis. The two review chapters on cerebrospinal fluid cytokines and on cellular immunity in slow viral infections are well written and referenced and provide interesting speculations.

The book would have been strengthened by having a review article in each broad subject area. Additionally, a question-and-answer or discussion section at the end of each chapter would have given the flavor of the discussions and interactions that took place at the symposium and that were enthusiastically referred to in the editors' introduction.

This book would hold much interest for those engaged in neuroimmunology research, but it is not comprehensive in its coverage of neuroimmunology. With the exception of the two review chapters, it is too specialized and would not hold great interest to a more general neurologic or medical audience.

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Neurologic Clinics, edited by William H. Theodore, 197 pp, with illus, $33, Philadelphia, Pa: WB Saunders Co, 1990.

Clinical Neuropharmacology represents the February 1990 issue of *Neurologic Clinics.* As with most issues in this series, only selected topics are chosen for review. The volume is not appropriate, therefore, for someone looking for a broad overview of clinical neuropharmacology. Eight chapters are included. The first two, "Basic Principles of Clinical Pharmacology" and "Clinical Trials," provide very good introductory material. The remainder of the chapters address specific neurologic disorders, including Parkinson's disease, hyperkinetic movement disorders, autonomic dysfunction, immune-related neuromuscular diseases, multiple sclerosis, head and face pain, sleep disorders, ischemic cerebrovascular disease, and epilepsy. Most chapters are clinically oriented, providing excellent and timely reviews of current approaches to therapy. The chapter on sleep disorders was disappointing in that it included only a very restricted discussion of sleep problems associated with Alzheimer's disease. This book is recommended for practicing neurologists, residents in training, and those interested in the specific topics covered.

Roger Kurlan, MD
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Vascular Brain Stem Diseases, edited by B. Hofferberth, G. G. Brune, G. Sitzer, H.-D. Weger, with illus, $53.50, New York, NY, S Karger AG, 1990.

This book provides a systematic and comprehensive review of brain-stem vascular diseases. It is divided into four sections—structural and functional basis, epidemiology and clinical aspects, diagnostic tools, and therapy. The section on structural and functional basis reviews the anatomic organization of the brain stem and describes the vascular supply of the brain stem and arterial variations, based on the extensive experience of the author with autopsy material. In addition, an excellent review of the mechanisms of posterior circulation ischemia is provided. The final chapter in the section discusses the vestibulo-ocular system and provides detailed schematic diagrams that aid in understanding this complex topic. The next section focuses on epidemiologic and clinical aspects of vertebrobasilar vascular disease. The first chapter reviews epidemiologic aspects and is complete with illustrative tables and angiograms. The following two chapters complement each other with a discussion of signs and symptoms of "vertebrobasilar insufficiency" and brain-stem stroke syndromes.

A complete section on diagnostic and laboratory tools used in the evaluation of vertebrobasilar occlusive disease discusses the fine points of the neurotologic examination, posturography, electronystagmography, evoked responses, continuous-wave Doppler sonography, transcranial Doppler sonography, specialized hematologic testing, and radiologic methods.

The last section discusses treatment of vertebrobasilar occlusive disease, including medical and surgical options. It includes an overview of medical treatments, detailed information about the use of thrombolytic therapy in animals and humans, and a review of surgical procedures used for vertebrobasilar disease.

Overall, the book is well edited, but the writing style varies from chapter to chapter. Some typographical errors and several figures that are upside down are a minor problem. This volume, the result of an international workshop on the topic of vascular brain-stem diseases, would be recommended to neurology residents and neurologists who care for patients who have suffered a stroke.

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Computational Neuroscience, edited by Eric L. Schwartz, 441 pp, with illus, $45, Cambridge, Mass, Massachusetts Institute of Technology Press, 1990.

This book is a collection of papers presented at a 1987 meeting that was, at least, partly intended to "define the field." It gathers papers from many of the most important contributors to computation neuroscience. Each author has written a chapter on some aspect of that author's work. Thus, this book is not intended as an introductory text. What it does provide, however, is a carefully written and well-edited presentation of many of the issues in computational neuroscience. It is particularly valuable because most chapters have been written from a broader perspective than one will find in the original literature. The chapters are grouped by the level of their approach (eg, synapse, network, neural map, or system). The book's structure is intentionally wide ranging and captures the diversity of the field. It might be fair to say that about the only sure unifying theme in *Computational Neuroscience* is its strong predisposition to describe the workings of the brain in quantitatively computable or mathematical terms. To most scientists there is a special appeal in mathematical models. This is particularly so when the mathematics is simple. However, even difficult models retain the appeal of explicitness.

Perhaps the most interesting dynamic in the field, and one that surfaces often in this book, is between the laboratory neuroscientists and the computer modeler. The modelers naturally want to produce "interesting" behavior from their models and are often willing to use simple approximations to neurons and synapses, ignoring a great deal of detail in the pursuit of greater computational realizability and simplicity of interpretation. Neuroscientists, just as naturally, insist that those neuroscientific details, wrested from the laboratories with such effort, should be included. In fact, many of the authors in this book are both laboratory scientists and computer modelers. Chapters by Gordon Shepard and Christof Koch are particularly insistent that the neuroscientific details are not yet well incorporated into most computational models.

Overall, this is a valuable volume to own, particularly so in a field as scattered about in the original literature as this. The articles are of very high quality and are faithful to their mission to be both computational and neuroscientific.

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Letters to the Editor

Letters to the editor should be submitted as an original and two duplicates. They should be typewritten double-spaced on plain bond paper; they will be subject to editing. If they are prepared on a word processor, do not justify the right margin. A copyright transmittal letter signed by all authors must accompany this (see "Instructions for Authors").

Seizures Following Carotid Endarterectomy

To the Editor. I read the article by Kieburtz et al[1] entitled "Seizures Following Carotid Endarterectomy" with interest, and find it to be a surprising addition to the neurologic literature. There is no doubt that many patients have seizures following carotid endarterectomy (CEA). What one might doubt is the speculation that seizures following CEA may be attributed to "cerebral hyperperfusion, cerebral embolization, or both" as suggested by Kieburtz and colleagues.[1] In looking through their experience of 650 CEAs from 1981 through 1987, they found seizures occurring in eight patients, just more than 1%. Olsen et al[2] reviewed "Epilepsy After Stroke" and found a 9% incidence of recurrent seizures in a prospective series of 77 consecutive stroke patients. Other studies of epilepsy following stroke were cited: 5% by Aring and Merritt,[3] 6% by Richardson and Dodge,[4] 8% by Louis and McDowell,[5] 6% by Marquardsen,[6] and 7% by Fentz.[7] It is, therefore, not surprising that patients undergoing CEA, many having had clinical or subclinical cerebrovascular accidents, should occasionally manifest seizures. That altered regional hemodynamics could trigger a seizure in a patient with cortical damage is a reasonable, if unproven, hypothesis. To be avoided is a suggestion that embolism or hyperperfusion per se are primarily responsible.

Reigel et al,[8] whose article is cited eight times by Kieburtz et al,[1] describe "cerebral hyperperfusion syndrome" in 10 patients, nine of whom had "clinical seizures"; the 10th had evidence of "subclinical seizures," ie, periodic lateralized epileptiform discharges (PLEDs) on electroencephalogram. Although descriptions of "seizures" are lacking, all 10 electroencephalograms are described as having shown "PLEDs." It is notable that PLEDs indicate an acute alteration of cerebral function and that although PLEDs can be seen in seizure patients, they are far from specific to that disorder. In fact, the most common cause in an elderly person is probably stroke.

If a significant number of seizures occurred during extracranial-intracranial bypass, that is, convulsions in patients without a clear embolic source for cortical infarction, hyperperfusion might be more reasonably implicated. That a small number of patients with stroke have seizures is well established; it is remarkable that so few occur in patients with CEA: 0.4% in the Mayo Clinic study[8] and 1% in the article by Kieburtz and coworkers.[1] Reigel et al[8] and Kieburtz et al[1] have added to our understanding of seizures, perhaps, in showing us that in a selected group of high-risk patients, seizures may occur less often than expected. I would not go so far as to suggest that the paucity of seizures in this group supports the notion, growing in popularity in recent years, that many of these patients do not have a disease that is benefited by surgery. The latter issue should be resolved as the results of ongoing controlled trials of carotid endarterectomy become available.

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1. Kieburtz K, Ricotta JJ, Moxley RT. Seizures following carotid endarterectomy. *Arch Neurol.* 1990;47:568-570.
2. Olsen TS, Hogenhaven H, Thange O. Epilepsy after stroke. *Neurology.* 1987;37:1209-1211.
3. Aring CC, Merritt HH. Differential diagnosis between cerebral hemorrhage and cerebral thrombosis: clinical and pathologic study of 245 cases. *Arch Intern Med.* 1935;56:435-456.
4. Richardson EP, Dodge PR. Epilepsy in cerebral vascular disease. *Epilepsia.* 1954;3:49-74.
5. Louis S, McDowell F. Epileptic seizures in nonembolic cerebral infarction. *Arch Neurol.* 1967;17:414-418.
6. Marquardsen J. *The Natural History of Acute Cerebrovascular Disease.* Copenhagen, Denmark: Munksgaard; 1969:1-192.
7. Fentz V. Epileptic seizures in patients with cerebro-vascular accidents. *Nordisk Medicin.* 1971;86:1023-1025. Abstract.
8. Reigel MM, Hollier LH, Sundt TM, et al. Cerebral hyperperfusion syndrome: a cause of neurologic dysfunction after carotid endarterectomy. *J Vasc Surg.* 1987;5:628-634.

In Reply.—In his letter, Sinoff asserts that seizures following carotid endarterectomy (CEA) occurred less frequently than expected in our study population. To substantiate his assertion he provides several references for the incidence of seizures following *stroke.* We suggest that not all patients having a CEA also have a stroke. A generous estimate of the incidence of stroke following CEA at our institution is 5%, based on prior reports from our institution and others.[1,2] Using this estimate for the incidence of stroke in patients with CEA, and using the incidence figures for seizure following stroke provided by Sinoff, 2.25 cases of seizures due to stroke following CEA would have been expected in our study population. This falls outside the 95% confidence interval for the observed number of eight cases of seizures following CEA, based on the binomial distribution. Therefore, we actually reported that seizures following CEA occurred *more* frequently than expected, if stroke were the sole cause of the seizures. We reiterate our previous statement that although there are several hypotheses regarding the mechanism of seizures following CEA (including embolization and hyperperfusion), the exact pathogenesis remains unclear.

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1. DeWeese JA, Rob CG, Satran R, et al. Endarterectomy for atherosclerotic lesions of the carotid artery. *J Cardiovasc Surg.* 1971;12:299-308.
2. Warlow C. Carotid endarterectomy: Does it work? *Stroke.* 1984;14:1068-1076.

Convergence Nystagmus Associated With Arnold-Chiari Malformation

To the Editor.—In the March 1990 issue of the Archives, Mossman et al[1] detailed the neuro-ophthalmologic findings of a convergence nystagmus associated with Arnold-Chiari malformation type I in a 17-year-old boy. This type of nystagmus, occurring usually with lesions of the pretectal region,[2,3] appeared only during neck movements and Valsalva's maneuver, and was absent in the primary position of gaze with the head in the neutral position. We congratulate the authors for the accuracy of the electro-oculographic and magnetic resonance imaging studies of the case, and we agree with their brilliant hypothesis that, even in the absence of an overt pretectal lesion, the appearance of convergence nystagmus might be explained on the basis of transient dysfunction of periaqueductal structures provoked by mechanical and/or hydrodynamic mechanisms occurring during neck movements and Valsalva's maneuver, ie, distortion of the aqueductal region and transient rise of cerebrospinal fluid pressure within the ventricular system. Our disagreement with the authors concerns, instead, the statement that the case studied showed the features of Arnold-Chiari malformation type I. Besides the depression of the lower poles of cerebellar tonsils up to C-2 and a moderate hydrocephalus involving the lateral and third ventricles, magnetic resonance imaging showed that the anterior recesses of the third ventricle, as well as of the fourth ventricle, were slightly distended, the brain stem was depressed, and the medulla appeared to be elongated with its anterior surface impressed by the tissues overlying the odontoid process. Furthermore, there was kinking of the cervicomedullary junction and a large syrinx extending from the level of C-3 to D-10. The hindbrain malformations revealed by magnetic resonance imaging do not resemble at all the anatomic features of type I Arnold-Chiari malformation. According to the original description of Chiari[4] and recent quantitative approaches to Chiari malformations with magnetic resonance imaging,[5] as well as several references quoted in the literature,[6-12] Arnold-Chiari malformation type I corresponds simply to a displacement, more or less pronounced, of the cerebellar tonsils into the upper cervical canal without caudal displacement of the medulla. Furthermore, although clinical presentation of Arnold-Chiari malformation type I often suggests a cerebellar and/or an upper cervical cord lesion, in some cases the malformation is asymptomatic and the diagnosis is occasional. We believe that to diagnose Arnold-Chiari malformation type I, any hindbrain anomaly different from Chiari's original definition is misleading.

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1. Mossman SS, Bronstein AM, Gresty MA, Kendall B, Rudge P. Convergence nystagmus associated with Arnold-Chiari malformation. *Arch Neurol.* 1990;47:357-359.

2. Segarra JM, Ojeman RJ. Convergence nystagmus. *Neurology.* 1961;11:883-893.

3. Nashold BS, Gills JP, Durham NL. Ocular signs from brain stimulation and lesion. *Arch Ophthalmol.* 1967;77:609-618.

4. Chiari H. Uber Veranderungen des Kleinhirns in Folge von Hydrocephalie des Grosshirns. *Dtsch Med Wochenschr.* 1891;17:1172-1175.

5. Aboulezz AO, Sartor K, Geyer CA, Gado MH. Position of cerebellar tonsils in the normal population and in patients with Chiari malformation: a quantitative approach with MR imaging. *J Comput Assist Tomogr.* 1985;9:1033-1036.

6. Achiron A, Kuritzky A. Dysphagia as the sole manifestation of adult type I Arnold-Chiari malformation. *Neurology.* 1990;40:186-187.

7. Appleby A, Foster JB, Hankinson J, Hudgson P. The diagnosis and management of the Chiari anomalies in adult life. *Brain.* 1968;91:131-140.

8. Bamberger-Bozo C. The Chiari II malformation. In: Myrianthopoulos NC, ed. *Handbook of Clinical Neurology: Malformations.* New York, NY: Elsevier Science Publishers; 1987;6:403-412.

9. Fish DR, Howard RS, Wiles CM, Simon L. Respiratory arrest: a complication of cerebellar ectopia in adults. *J Neurol Neurosurg Psychiatry.* 1988;51:714-716.

10. Gilbert JN, Jones KL, Rorke LB, Chernoff GF, James HE. Central nervous system anomalies associated with meningomyelocele, hydrocephalus, and the Arnold-Chiari malformation: reappraisal of theories regarding the pathogenesis of posterior neural tube closure defects. *Neurosurgery.* 1986;18:559-564.

11. Halpin DMG, Trend P, Symon L, Harding AE. Type I Arnold-Chiari malformation in a 77-year-old woman. *Arch Neurol.* 1990;53:88-89.

12. Paul KS, Lye RH, Strang FA, Dutton J. Arnold-Chiari malformation: review of 71 cases. *J Neurosurg.* 1983;58:183-187.

In Reply.—We are pleased that your correspondents agree with our description of the abnormalities and of the implications drawn from them and that disagreement is confirmed to our categorization of the patient as a Chiari type I malformation.

It is true that in Chiari's original description of the type I malformation only the cerebellar tonsils are displaced inferiorly, and it is therefore historically correct to include only cases of pure cerebellar ectopia in the Chiari type I category. However, one is then left with a large majority of patients in whom depression of the cerebellar tonsils is associated with varying degrees of depression of the medulla. In some of these cases there is a typical cervicomedullary kink at the level of the depressed dorsal column nuclei. Syrinx formation is commonly present. If these are not to be classified as Chiari type I malformations, what is the correct terminology? They certainly do not fit into the category of Chiari type II malformations in which the fundamental abnormality is incomplete formation of the pontine flexure. In Chiari type II malformations there is elongation of the pons and medulla and malformation of the cerebellar vermis, the hindbrain extending down into the cervical canal with the nodulus at the leading edge of the depressed cerebellum. This malformation also is associated with syringomyelia or hydromyelia, and almost always with dysraphism, usually meningomyelocele.

It is evident that in depression of the medulla, in addition to the tonsils, it is not always a malformation, but a deformation secondary to compression of the posterior fossa contents. This may occur, for example, in severe craniostenosis or in the type of basilar invagination with convexobasia associated with osteogenesis imperfecta, and it is likely that many other cases termed Chiari type I malformations are in truth acquired deformities. However, even if cases with medullary in addition to tonsillar depression do not strictly conform to Chiari's original description, we believe that they are fundamentally different from the type II malformation and can reasonably be considered as an extension of type I. It would be facetious and inaccurate to refer to them as Chiari type 1.5, but to do so would draw attention to the dilemma caused by the eponymous terminology.

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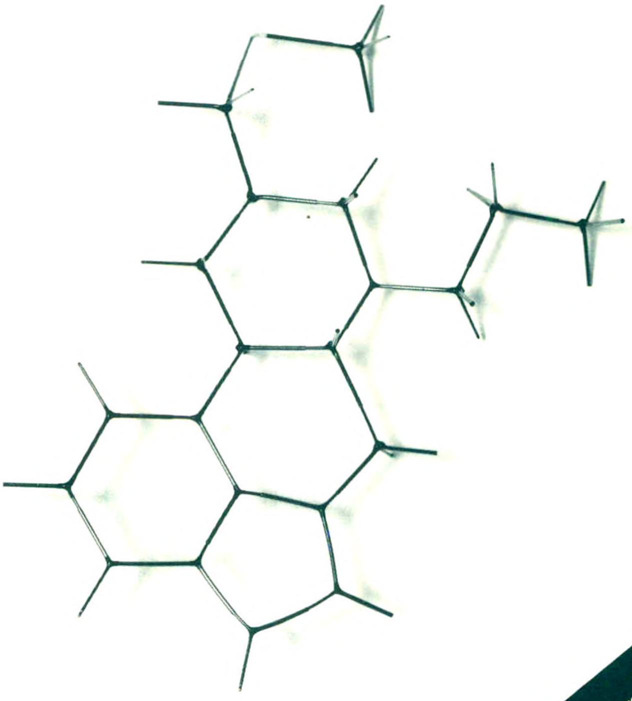

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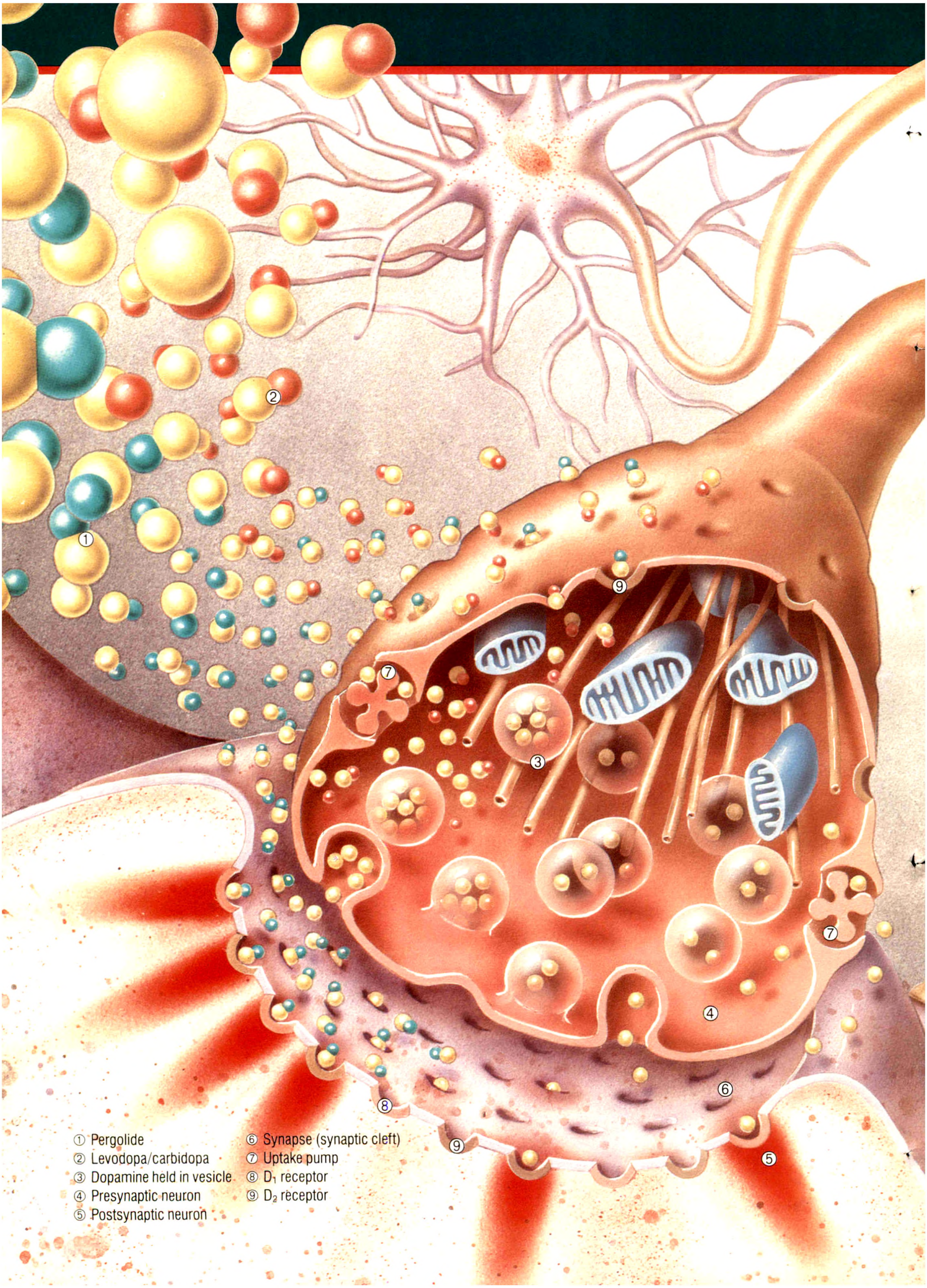
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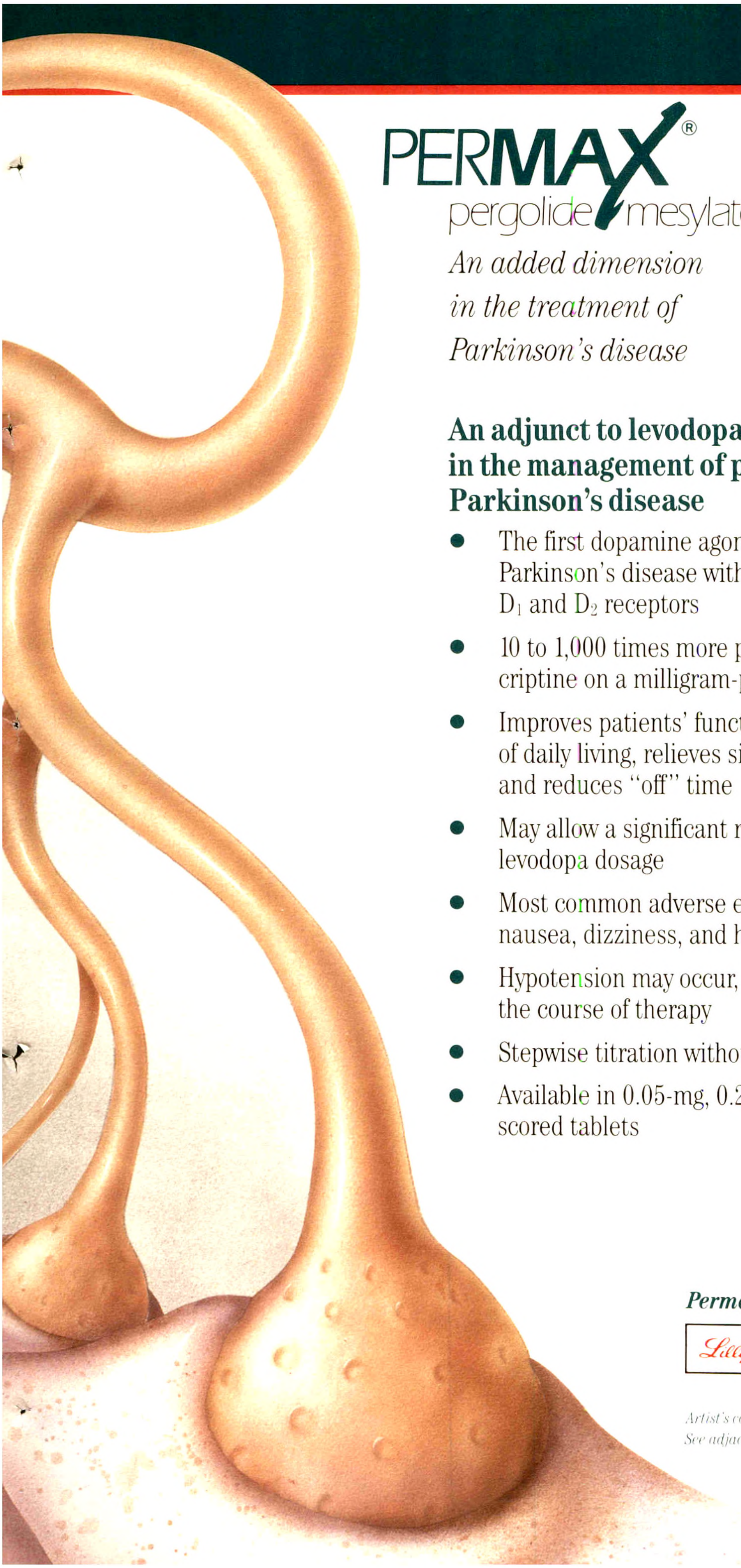

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Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities –*See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Events	
Body System/ Adverse Event*	Pergolide Mesylate N=189	Placebo N=187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax —This section reports event frequencies evaluated as of October 1988 for adverse events ocurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome

Cardiovascular System —*Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly

Metabolic and Nutritional System —*Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusion, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder

Urogenital System —*Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding

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Results of Surgery for Extratemporal Partial Epilepsy That Began in Childhood

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• Thirty-five consecutive patients who underwent surgery for intractable extratemporal seizures originating in childhood are described. Candidates for surgery were selected on the basis of clinical criteria, neurodiagnostic imaging, and an electroencephalographic investigation that included the use of sphenoidal electrodes and long-term monitoring. Invasive preoperative monitoring was not used. Our results, with respect to the control of seizures and behavioral improvement, are comparable with series in which data from invasive recordings were used in the selection process. Sixty-three percent of the 35 patients (76.5% of those operated on after the introduction of long-term electroencephalographic monitoring) became either seizure free or experienced a reduction in their frequency of seizures by at least 75%. The favorable outcome in this group of patients strengthens the argument for early operation in children with intractable epilepsy, even when the seizure focus is outside the temporal lobe.

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Surgery for seizures that began in childhood, and neurosurgery itself, was born on May 25, 1886. On that date, an innovative 29-year-old English surgeon nicknamed Archibald Allright, which is perhaps a clue to his skill and optimism, performed his first operation on the human brain and the first operation ever for epilepsy. The patient, referred by Hughlings Jackson, was a 22-year-old whose seizures began in childhood and occurred as frequently as 3000 per fortnight.[1,2] Although the patient was seizure free postoperatively, the follow-up was short by current standards—3 months at the time of the report. Professor Charcot, visiting from Paris, France, on hearing the presentation of this and two other cases, congratulated the surgeon, Victor Horsley, for having cured epilepsy by operation.[1] The core element of surgery for epilepsy, excision of the epileptogenic complex, has not changed from that date. What have changed and continue to change are our methods and rationale for selecting patients for surgery, the operative techniques, and our analysis of surgical results.

"Seizures are frightening, cause damage, and are a major contribution to social isolation,"[3] yet the traditional approach to epilepsy in children has tended toward nonoperative management, probably because seizures in some children, unlike those in adults, can be self-limiting.[4] As a result, children with recalcitrant seizure disorders who may profit from surgery often have this therapy delayed unnecessarily or withheld.[5-7] Even for patients who undergo this treatment, the selection process and the surgical techniques vary appreciably among medical centers,[8] and the optimal age for intervention remains uncertain.

Surgery in carefully selected children reduces or eliminates seizures and facilitates social adaptation[9,10]; however, nearly all published series of operations for epilepsy in the pediatric age group have been dominated by temporal lobectomies.[11-14] Because temporal lobectomy consistently yields more favorable results than other anatomically defined cortical resections,[15-17] results from the reported series are not representative of results for the more challenging extratemporal locations. This report will focus on our experience with the surgical management of chronic epilepsy due to extratemporal cortical seizure foci identified by noninvasive means, ie, without preoperative dural or depth recordings.

PATIENTS AND METHODS

All patients who underwent surgery at The Children's Hospital, Boston, Mass, between January 1972 and August 1987 for chronic, extratemporal, partial epilepsy originating in childhood are the basis of this report. Patients with hemispheral abnormalities who underwent extensive cortical resections are included; those who had temporal lobectomy or hemicorticectomy are excluded. We placed no limit on age at the time of surgery but required that the epilepsy begin within the pediatric age group, ie, before 16 years of age. Except for children younger than 2 years of age, we excluded those whose epilepsy had been present for less than 2 years. Although not all patients were children at the time of surgery, the median age at operation was 15 years. There was no apparent change in the pattern of referral of our patients during the accrual of this series, and our series is relatively uniform with respect to the neurologists and neurosurgeons involved, the operative techniques employed, and the fact that implanted electrodes (depth, epidural, or subdural) were not used. Consequently, we believe that this series is representative of the contemporary experience with intractable extratemporal partial epilepsy in children who are appropriate candidates for surgical intervention.

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Table 1.—General Characteristics and Aggregate Results of Surgical Treatment

General Characteristics	
M/F, 20/15	
L/R, 14/21	
Age at onset of seizures, y	1 m-15; median, 4.0; mean, 5.1
Age at operation, y	2-33; median, 15.0; mean, 14.5
Duration of seizures, y	1-24; median, 7.2; mean, 9.4
Duration of follow-up, y	3.6-19; median, 9.2; mean, 10
Postoperative Seizure Scores (Mean, 2.6)	
Grade	**N (%)**
0, no improvement	4 (11.4)
1, slight improvement (~ 25%)	7 (20.0)
2, moderate improvement (~ 50%)	2 (5.7)
3, near complete improvement (≥75%)	8 (22.9)
4, seizure free†	14 (40.0)
Postoperative Performance	
Type of Change	**N (%)**
Worse	1 (2.8)
No change	19 (54.3)
Improved but with new deficits	2 (5.7)
Improved	13 (37.1)

*Treatment administered to 35 consecutive patients who underwent surgery for extratemporal partial epilepsy that began in childhood.

†Receiving or not receiving medication.

All patients had received multiple trials of anticonvulsant medications and were referred for management of recalcitrant seizure disorders. Each patient was restudied at our institution with extensive electroencephalography (EEG), which included provocative and localizing tests (intravenous thiopental,[18] diazepam,[19] or methohexital[20]) in most patients. Nasopharyngeal electrodes were placed for basal EEG recording after 1972; sphenoidal electrodes, as well as other special electrodes, were used after 1979. Long-term monitoring for the purpose of recording multiple seizures became available in 1981. No patients in this series underwent invasive preoperative investigations, such as implanting dural strip electrodes or having depth electrodes implanted on a long-term basis.

All patients underwent the following intensive neuroradiologic testing: pneumoencephalography before 1974, computed tomography (CT) after 1974, and, more recently, magnetic resonance imaging (MRI). An attempt to identify discrete radiographic abnormalities was made in each case. The radiographs of all patients whose studies were considered to be negative at the time of surgery were reviewed again at the time of this investigation. Neuropsychological testing[21-23] was administered before and after surgery in all patients, including the very young children. Intracarotid injection of amobarbital sodium[24] for lateralization of speech and for testing of memory[22] was performed preoperatively in patients in whom this information was deemed useful and who were sufficiently cooperative.

Surgery was recommended on an individual basis, not according to a fixed protocol. General anesthesia was employed in all cases in this series. After opening the dura and exposing the surface of the brain, electrocorticography was performed with a 16-channel instrument (model 8, Grass Instruments, Quincy, Mass) both to confirm the localization of abnormalities identified preoperatively on noninvasive EEGs and to guide the extent of surgical resection. During electrocorticography, methohexital was often injected intravenously to precipitate or enhance abnormalities previously seen on EEG.[20] Cortical stimulation was not used. In general, standard surgical techniques were employed. When a neoplasm was encountered, the operative technique was modified as needed in an attempt to achieve total resection. In general, the extent of the resection in patients with neoplasia was guided by the surgeon's ability to identify abnormal tissue. Cortex overlying tumor was resected and, if electrocorticography then revealed persistent seizure foci in surrounding cortex, the electrophysiologically abnormal tissue was then also removed (if the area was considered safe for resection).

All operative specimens were processed in routine fashion by the department of pathology (neuropathology) of The Children's Hospital, and a histopathologic analysis was obtained in all cases.

Patients received anticonvulsant medications in the immediate postoperative period; these medications were reduced when warranted, based on clinical features and findings on EEG. When the epilepsy remained poorly controlled, a second operation was performed.

Postoperative follow-up was primarily at The Children's Hospital. All available information on the control of seizures, including observations by patients' families and reports from the referring physicians, was collected for each patient. The following scale was used to quantitate the effectiveness of surgery: 0, no definite improvement; 1, slight improvement (approximately 25%); 2, moderate improvement (approximately 50%); 3, near complete control with only rare seizures (at least 75% improvement); and 4, total seizure control (with or without medications). This score reflected the frequency of seizures throughout the postoperative period (after the last operation in those patients having two operations). Convulsive attacks in the immediate postoperative period and those clearly related to withdrawal of anticonvulsant therapy were not considered. For patients with several years' follow-up, the grading reflected the frequency of seizures in the few years immediately preceding this survey. When a patient had two seizure patterns and a different response to surgery for each, the average change was recorded. Because of the inherent error in quantitating small improvements in seizure control and because small improvements may not be very beneficial to the patient, we have considered "significant improvement" to be a reduction of at least 75% (ie, scores 3 and 4).

Postoperative performance, incorporating both social functioning and the results of neuropsychological testing, was evaluated, and each patient was given a performance rating. The purpose of the performance rating was to assess changes in intellectual and social behavior that were not directly dependent on the control of seizures. For example, a patient who was a good student despite frequent seizures and who remained a good student after surgery, albeit without seizures, was classified as having no change in performance. Changes in performance were usually best documented in the results of neuropsychological testing, but sometimes change was most apparent in reports from school, employer, or parents. Using the preoperative condition as a baseline, the following categories were used to rate performance: W, worse; NC, no change; M, improved but with new and unexpected neurological deficits; and I, improved.

RESULTS

Thirty-five patients who underwent 39 operations for epilepsy form the basis of this report. The characteristics of the whole group and the aggregate results of surgery are presented in Table 1. Sixty-three percent of patients became either seizure free or experienced a significant reduction in the frequency of seizures. No patient's seizure disorder was made worse by that patient's undergoing an operation, and only four patients (11%) failed to have some improvement in control of seizures.

The first 18 patients (operated on before January 1, 1980) had a mean postoperative seizure grade of 2.2, and 50% of these patients experienced a significant improvement in control of seizures (score 3 or 4); the subsequent 17 patients had a mean postoperative seizure grade of 2.9 and 76% had a significant improvement in control of seizures. The postoperative performance rating, however, was approximately the same in the two periods—39% of the first 18 patients were improved vs 47% of the latter. Overall, the performance rating after surgery was improved in 15 patients (43%), although two of these had new neurologic deficits. Two patients had a worse postoperative performance rating: one had chronic encephalitis and another had a pre-existing contralateral frontal injury from radiation therapy; behavioral deficits developed following removal of an extensive region of porencephaly and cicatrix due to tumor removal years before.

Outcome by Anatomic Location

The general characteristics of the patients, when grouped by location of cortical resection and the results of surgical treatment, are presented in Tables 2 and 3.

Table 2.—General Characteristics and Results of Surgery by Location of Cortical Resection

Characteristic	Frontal, n (%)	Parietal, n (%)	Occipital n (%)	Multilobar§ n (%)
		General Data		
N (%)	14 (40)	3 (8.6)	5 (14)	13 (37)
M/F	8/6	1/2	3/2	7/6
L/R	3/11	2/1	3/2	6/7
Age at onset of seizures*	3	0.25	9	4
Age at operation*	12.2	12.6	16.6	17
Duration of seizures*	7.8	8.1	5.6	10.1
Length of follow-up*	8.2	8.0	8.1	6.5
		Postoperative Grade and Performance		
Seizure grade				
Mean values	2.9	4.0	2.8	1.9
Significantly improved (grades 3 plus 4)	9 (64)	3 (100)	4 (80)	6 (46)
Performance†				
No. worse	1	. . .	. . .	1
No. improved‡	3	2	3	6

*Median in years.

†Patients whose postoperative performance was unchanged have been omitted.

‡Includes patients with new neurologic deficit after surgery (ie, group I [improved] + group m [improved with new neurologic deficit]).

§May include excision of temporal lobe with extratemporal cortex.

Table 3.—Results by Type of Pathologic Findings by Location of Cortical Resection

Location of Cortical Resection	N	Pathologic Findings, No.	Seizure Grade*					Performance Rating†			
			0	1	2	3	4	W	NC	M	I
Frontal	14	Tumor, 6	1	. . .	. . .	1	4	. . .	5	. . .	1
		Atrophy, 1	. . .	. . .	. . .	. . .	1	1	. . .	. . .	. . .
		Cortical malformation, 2	. . .	. . .	1	. . .	1	. . .	2	. . .	. . .
		Vascular malformation, 1	. . .	. . .	. . .	. . .	1	. . .	. . .	. . .	1
		Nonspecific, 4	. . .	2	1	. . .	1	. . .	3	. . .	1
Parietal	3	Cortical malformation, 2	. . .	. . .	. . .	. . .	2	. . .	1	. . .	1
		Vascular malformation, 1	. . .	. . .	. . .	. . .	1	. . .	. . .	. . .	1
Occipital	5	Tumor, 1	. . .	. . .	. . .	1	. . .	. . .	. . .	1	. . .
		Atrophy, 1	. . .	. . .	. . .	1	. . .	. . .	. . .	. . .	1
		Cortical malformation, 1	. . .	. . .	. . .	1	. . .	. . .	. . .	. . .	1
		Vascular malformation, 1	. . .	. . .	. . .	. . .	1	. . .	1	. . .	. . .
		Nonspecific, 1	. . .	1	. . .	. . .	. . .	. . .	1	. . .	. . .
Multilobar‡	13	Tumor, 4	1	2	. . .	. . .	1	. . .	3	. . .	1
		Atrophy, 3	. . .	1	. . .	2	. . .	. . .	. . .	1	2
		Cortical malformation, 1	. . .	. . .	. . .	1	. . .	. . .	. . .	. . .	1
		Sturge-Weber syndrome, 1	. . .	. . .	. . .	. . .	1	. . .	. . .	. . .	1
		Encephalitis, 2	1	1	. . .	. . .	. . .	1	1	. . .	. . .
		Nonspecific, 2	1	. . .	. . .	1	. . .	. . .	2	. . .	. . .
Total	**35**		**4**	**7**	**2**	**8**	**14**	**2**	**19**	**2**	**12**

*See Table 1 for definitions of grades.

†W indicates worse; NC, no change; M, improved with new neurologic deficit; and I, Improved.

‡May include excision of temporal lobe with extratemporal cortex.

Frontal Lobe.—Control of seizures was significantly improved in nine of 14 patients who underwent frontal resection (64%). Eight patients (57%) became seizure free; three of the nine had an improved performance rating; and one was worse (frontal syndrome). The one patient with no apparent benefit (grade 0) from frontal corticectomy had a large tumor that could not be totally removed. Four patients had a postoperative seizure grade of 1 or 2; two of these underwent an operation on the basis of interictal EEG foci without corresponding abnormalities on neurodiagnostic imaging. The third patient had a focal abnormality on CT but no clear focus on EEG. The fourth patient had nonspecific pathologic lesions and was operated on while in status epilepticus (epilepsia partialis continua). None of the five patients without significant improvement had preoperative long-term monitoring of ictal events.

Parietal Lobe.—All three patients had excellent control of seizures after surgery and two had improved performance ratings.

Occipital Lobe.—Four of five patients (five different pathologic findings) had significantly improved control of seizures. The one who did not improve had nonspecific pathologic findings and presented with epilepsia partialis continua. The performance rating improved in three patients and was unchanged in two.

Multilobar.—Six (46%) of 13 patients had postoperative seizure grades of 3 or 4 and six patients had an improved performance rating after surgery. Five of seven patients with little or no improvement in seizure control had incomplete removal of their lesions. The one patient with a worse postoperative performance had relentlessly progressive chronic encephalitis.

Outcome by Pathologic Abnormality

All surgical specimens contained histopathologic abnormalities (Tables 3 through 5 and the Figure). The 35 cases can be grouped into seven categories on the basis of gross and histologic features.

Tumor.—Eleven patients (31%) had intractable epilepsy attributable to neoplasia; the anatomic distribution of these tumors is shown in Table 6, and the distribution of histologic types is displayed in the Figure. Seven patients (64%) had improved seizure control, four (36%) of whom became seizure free. Control of seizures was not related to type of tumor but rather to the extent of removal and to the degree of malignancy. The two patients in whom postoperative improvement in seizures was absent (score, 0) had large and incompletely resected tumors. Their performance rating is summarized in Tables 3 and 5.

Atrophic and Cicatricial Lesions.—This pathologic category accounted for five patients (14% of the total), and the control of seizures was significantly improved in four of them (80%). Four of the five had porencephaly; three of

Table 4.—General Characteristics and Results of Surgery by Type of Pathologic Findings

Characteristic	Tumors, n (%)	Atrophy, n (%)	Cortical Malformations, n (%)	Vascular Malformations, n (%)	Sturge-Weber Syndrome, n (%)	Encephalitis, n (%)	Nonspecific, n (%)
N (%)	11 (31)	5 (14)	6 (17)	3 (8.6)	1 (2.9)	2 (5.7)	7 (20)
M/F	5/6	3/2	5/1	1/2	0/1	2/0	4/3
L/R	5/6	4/1	2/4	0/3	0/1	1/1	2/5
Age at onset of seizures*	4	4	0.25	9	3.5	12	6
Age at operation*	12	19	8.6	17.2	7.8	18	17
Duration of seizures*	7.1	15.2	7.3	8.3	4.3	6.7	13
Duration of follow-up*	8.9	8.9	7.9	9.3	6.6	18	9.5
Postoperative seizure score							
Mean value	2.5	2.6	3.3	4.0	4.0	0.5	1.7
No. improved (grades 3 plus 4)	7 (64)	4 (80)	5 (83)	3 (100)	1 (100)	0 (0)	1 (14)
Postoperative performance†							
Worse	0	1	. . .	. . .	. . .	1	0
Improved‡	3	4	3	2	1	. . .	1

*Median in years.

†Patients whose postoperative performance was unchanged have been omitted.

‡Includes patients with new neurologic deficit after surgery (ie, group I [improved] + group M [improved with new neurological deficit]).

Table 5.—Results by Type of Pathologic Findings

		Seizure Grade					Performance Rating*			
Pathologic Findings	N	0	1	2	3	4	W	NC	M	I
Tumor	11	2	2	. . .	2	5	. . .	8	1	2
Atrophy	5	. . .	1	. . .	4	. . .	1	. . .	1	3
Cortical malformation	6	. . .	. . .	1	2	3	. . .	3	. . .	3
Vascular malformation	3	. . .	. . .	. . .	. . .	3	. . .	1	. . .	2
Sturge-Weber syndrome	1	. . .	. . .	. . .	. . .	1	. . .	. . .	. . .	1
Encephalitis	2	1	1	. . .	. . .	. . .	1	1	. . .	. . .
Nonspecific	7	1	3	1	1	1		6		1
Total	**35**	**4**	**7**	**2**	**9**	**13**	**2**	**19**	**2**	**12**

*W indicates worse; NC, no change; M, improved with new neurologic deficit; and I, improved.

the five had an extensive multilobar resection and one had an occipital lobectomy. Patients with atrophic lesions had a high proportion of postsurgical improvement in performance (four [80%] of five improved). None of the patients became seizure free, but four of five had at least a 75% reduction in seizures and also a significant improvement in performance.

Vascular Malformations.—All three patients became seizure free; performance was improved in two patients and one patient experienced no change. None had experienced a clinically apparent hemorrhage.

Cortical Malformation—Hamartoma and Tuberous Sclerosis.—Five of six patients had a significantly improved seizure score, and three of these patients are seizure free. Three had an improved performance rating and the remainder were unchanged.

Chronic Encephalitis.—One of two patients presented with epilepsia partialis continua and postoperatively experienced a relentless progression, sufficient to necessitate institutionalization; the other patient's condition remained stable but the epilepsy was not improved. Two other patients (ie, two not classified as having chronic encephalitis) presented with epilepsia partialis continua, and their surgical specimens had gliosis and perivascular cuffing but not neuronophagia or glial nodules. Although these abnormalities could represent the residua of encephalitis, these two patients were included in the nonspecific group.

Nonspecific Abnormality.—Two (29%) of seven patients with this pathologic diagnosis had significantly improved seizure control. One patient had an improved performance rating, six patients had ratings that were unchanged, and no patient's ratings were worse. Gliosis was the most common nonspecific histologic feature; it was present in seven cases. Gliosis was associated with neuronal loss in two patients and calcification in one. Three of these patients had evidence of focal atrophy on CT, and in one bilateral dilatation of the temporal horns was noted. No apparent relationship between postoperative control of seizures and either the radiographic appearance or the histologic findings in these patients was seen.

Epilepsia Partialis Continua

Three patients had epilepsia partialis continua for an average of 2.3 years before surgery. Cortical resections were in the occipital, frontal, and frontoparietal regions. One patient had the typical histologic features of encephalitis; the other two patients had nonspecific histologic changes. After the operation, none of these patients had any significant change in the character or frequency of the epilepsia partialis continua.

Table 6.—Anatomic Distribution of 11 Neoplasms*

Site	N (%)
Frontal lobe	6 (54)
Occipital lobe	1 (9)
Frontoparietal region	1
Parieto-occipital region	2 (36)
Parietotemporal region	1
Total	**11 (99)**

*Sample is from 35 patients who had undergone surgery for chronic extratemporal partial epilepsy that began in childhood. Sum of percentages is less than 100 due to rounding.

Anticonvulsant Therapies

At the close of this study, five patients (14%) were receiving no anticonvulsants; clearly, these patients had good results from surgery and were seizure free. Twelve patients (34%) required fewer anticonvulsants or smaller dosages after surgery. Therefore, 17 patients (49%) required less medication or no medication as a result of the surgical intervention. The number and quantity of anticonvulsants did not change significantly after surgery in 18 patients. Nine of 22 patients whose recent surgery was successful (grade 3 or 4) are still receiving anticonvulsants but are candidates for reduction or discontinuance of medications.

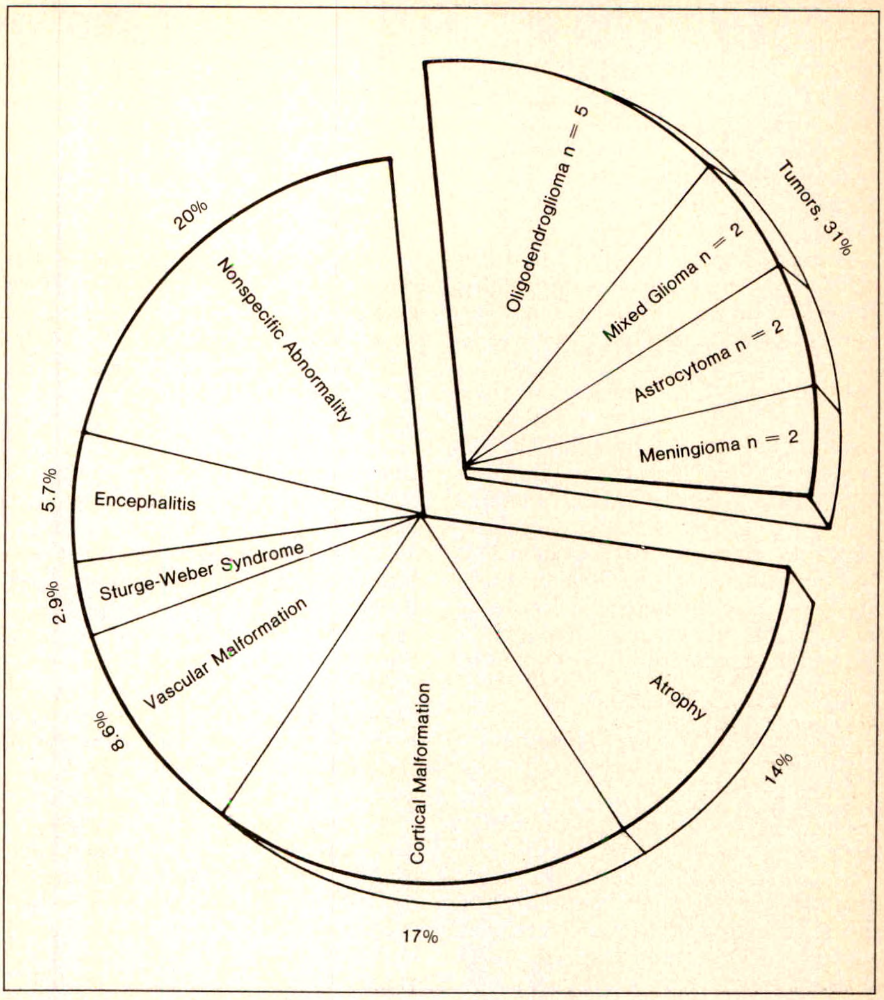
Other Operations

Four patients had two operations for epilepsy at The Children's Hospital during the time encompassed by this series, and for each patient the initial poor result was attributed to insufficient resection of epileptogenic cortex or tumor. The interval between operations ranged from 2 weeks to 5.8 years and averaged 1.8 years. The second operation yielded good results (seizure grade, 4) in two patients and minimal improvement in two others.

Two children in this series underwent brain biopsies prior to referral to The Children's Hospital. One, a child with a postherpetic cicatrix, had improved seizure control after cortical resection; the other had nonspecific pathologic changes and a poor surgical result. Another patient, who had chronic encephalitis, had a cortical resection at another institution 11 years after our initial operation; this second operation was without benefit.

Complications

Two patients were hemiparetic after surgery but improved sufficiently to be fully ambulatory. In both, the hemiparesis can be attributed to the extent of cortical resection required to remove a tumor. Visual field deficits following either temporal or occipital lobectomy were expected sequelae and were not considered to be complications. Hemianopia as a result of the removal of an occipital oligodendroglioma developed in one child; he became seizure free, but the visual field defect may have contributed to his being in a severe motor vehicle accident. No operative deaths occurred. Aseptic meningitis occurred in one patient. Complications not involving the nervous system included two patients with wound infections, two patients with postoperative hematomas, and one patient with thrombosis within the deep-venous system of one lower extremity.



Distribution of pathologic processes in 35 consecutive patients who underwent surgery for extratemporal epilepsy that began in childhood and who were selected for surgery by noninvasive criteria. The category of neoplasia is subdivided by specific tumor types.

Neuroradiology

Although many of these patients had no abnormality recognized on preoperative neurodiagnostic imaging, 27 (77%) of 35 had some identifiable abnormality on retrospective review. One or more neuroradiologic abnormality was present in each of 11 patients with neoplasia; five had a small localized mass affect, three had subtle mineralization, and five had an area of abnormal (low or high) density on CT. The neuroradiologic abnormalities in the brains of children with porencephaly were also diagnostic. Cerebral atrophy and cortical calcification were apparent on CT in the patient with Sturge-Weber syndrome.[25] Every patient with tuberous sclerosis had a radiographically apparent mass. The eight patients in this series without any (even very small) abnormality on retrospective review of neurodiagnostic imaging had the following pathologic diagnoses: nonspecific abnormality in four patients, cortical malformation (hamartoma) in two patients, and encephalitis in two others.

The postoperative mean seizure grade was 1.7 in patients without abnormality on neurodiagnostic imaging and 2.7 in those with abnormality.

COMMENT

Our observations indicate that among children with intractable seizures good results can follow corticectomy for extratemporal epileptic foci, using only noninvasive diagnostic methods for selection. Overall, 88.6% of our 35 patients experienced some improvement in the control of their epilepsy, and 62.9% had a good-to-excellent outcome (40% seizure free and 22.9% with only occasional seizures). If we consider only the later half of our study (those who underwent an operation after December 31, 1980), ie, the group operated on after CT and long-term monitoring with sphenoidal electrodes became available and hence the group most representative of our current selection of cases, 76.5% had a reduction in seizures of at least 75%. Benefit also came in terms of an improved ability to function in daily activities.

Most surgical series report good-to-excellent results in 70% to 90% of patients; however, such results are strongly biased by the very good outcome in patients undergoing temporal lobectomy.[11-14] The fact that extratemporal resections do not have nearly as good results[15-17] may explain why so little has been written about these patients. Compared with the information available on adults who underwent an operation for extratemporal partial epilepsy, our results, especially after 1980, are quite favorable.

Forty-three percent of our patients had an improved performance rating after surgery, in addition to improved control of seizures. Improvement in performance probably relates to patients having fewer seizures and/or their requiring less anticonvulsant medication (true for over 50% of our patients). Most who did not improve ("no change" category) were functioning well before surgery and, therefore, could not improve. Two patients had worse postoperative performance ratings; one had histologic evidence of encephalitis and the other had a frontal lesion contralateral to the site of the operation.

Noninvasive vs Invasive Preoperative Evaluation

Recently published studies of surgery for epilepsy have emphasized the value of invasive preoperative monitoring in the selection of patients.[13,26-32] Invasive testing with depth electrodes and/or surface recordings (subdural or epidural) requires additional surgical procedures, is expensive, and has associated risks of morbidity (eg, hemorrhage or infection).[33] Furthermore, many pediatric patients have a low tolerance for the usually long monitoring periods required.[13,29,30,32,34] We recognize the value of invasive preoperative monitoring in selected patients,[13,28-32] but it is important to identify the patients in whom these procedures can be avoided. Extracranial recordings made during multiple spontaneous seizures provided, in our patients, a reliable basis for localization of epileptic foci. The information that we obtained by careful analysis of ictal events recorded from the convexity and base of the skull via noninvasive techniques[35,36] and that obtained from intraoperative electrocorticography proved to be sufficient to guide surgical resection. Although the risk of erroneous localization or lateralization when relying heavily on extracranial electroencephalographic data is always present,[13] it is noteworthy that such events did not occur in our 35 consecutive patients who underwent surgery. Concordant structural anomalies on neuroimaging, which we did not require but frequently found, undoubtedly minimized this risk. Other criteria that influenced our selection of patients for surgery were constancy of an interictal EEG focus over several years[37] and clear compatibility of the neurologic and electrophysiologic findings with the functional profile obtained from neuropsychological assessment.[21-23] Consequently, without using invasive monitoring our results compare favorably with the published results from centers where recordings from depth or subdural electrodes weighed heavily in the selection of patients. Our experience is consistent with the view expressed by Ojemann and Engel,[38] Gloor,[39] and Olivier et al[30] that the risk-to-benefit ratio of investigation with depth electrodes should be carefully evaluated in each case and is rarely, if ever, required in patients who have both a structural abnormality on neurodiagnostic imaging and a corresponding epileptogenic focus in the EEG.

Our selection of cases improved over the time of accrual, as evidenced by the higher postoperative seizure scores in the latter half of the series (76.5% significantly improved). While some of this improvement may be attributed to learning from our own experience and the published experiences of others, we believe that most of the improvement is attributable to the introduction of long-term EEG monitoring and to advances in neurodiagnostic imaging.[40] These new technologies permitted better patient selection via more accurate localization of surgically accessible epileptogenic foci that, in turn, led to greater operative success. Future advances in neuroradiologic imaging, especially MRI[41-43] and positron emission tomography,[44-46] will probably enhance our ability to define anatomically epileptogenic foci and may restrict the need further for invasive electroencephalography.

Recording from depth and/or epidural electrodes can be helpful in discriminating an orbitofrontal focus from a focus in the mesial temporal lobe, however, during the span of this series we encountered this problem in only three patients. In two of these patients (operated on elsewhere and, therefore, not included in this study), recordings from epidural strip electrodes over the frontal and temporal convexity did not prevent false localization; a subsequent temporal lobectomy did not alter the frequency of seizures. However, in the third case, depth electrodes identified an orbitofrontal focus, and the patient did well after cortical resection. It is possible that some patients who would have benefited from surgery were not offered an operation because a focus that could have been identified by invasive recording was missed, ie, they were erroneously thought to have generalized epilepsy. While this possibility cannot be excluded, we believe that such cases were rare or nonexistent in our population of patients with seizures.

Most failures in surgery for epilepsy, whether dictated by pathology and anatomy, or secondary to an intentional conservative surgical approach, have been ascribed to insufficient localization and/or inadequate resection[47,48]; this is consistent with our experience. Therefore, we believe that the surgical failures encountered in this series after the introduction of long-term surface and basal EEG monitoring would probably not have been avoided by more invasive investigations. It is possible, however, that a few failures and the occasional need for a second operation could have been prevented by more extensive or better tailored resections guided by preoperative depth electrode encephalography, intraoperative stimulation of the cortex under local anesthesia, or preoperative mapping of the eloquent areas via implanted subdural grid electrodes.[13,30-32,38,41,49] When a discrepancy exists between EEG findings and neuroimaging or, in patients with negative neuroimaging, between neurological observations and the EEG findings, then invasive monitoring seems mandatory. Also, the existence of multilobar lesions in patients not qualifying for hemispheral surgery is another clear indication.

It is widely believed, contrary to our observations, that neuroradiographic abnormalities in patients with intractable epilepsy are rare unless there is a mass.[13,50] However, subtle but definite enhancement can often be recognized on CT in patients with nonneoplastic epileptogenic foci in frontal lobes, when no abnormality is apparent on the noncontrasted images.[42] In Goldring's[51] series, seizure foci were localized with radiographic studies in five of 10 patients, and, in other cases, "partial localization" was achieved. These observations would seem to indicate that neurodiagnostic imaging can have an extremely important role in the preoperative evaluation of patients with partial epilepsy.[40] Retrospective review of preoperative neuroimaging revealed that over 75% of our patients had focal, usually nondiagnostic, radiographic abnormalities that correlated with the EEG localization. Such a large percentage is probably a reflection of the pathologic findings (eg, tumors, malformations, and atrophic lesions) that were common in our population and, perhaps more frequently, the cause of chronic intractable epilepsy in children. In the absence of focal lesions, a lateralizing radiographic abnormality (eg, atrophy) was common and often provided reassuring corroboration of EEG localization.

Frontal Lobe Epilepsy

Most series of surgically treated epilepsy, especially that beginning in childhood, report small numbers of frontal lobe operations[7,52,53]; only 10% of operations for seizures at the Montreal (Quebec) Neurological Institute involved the frontal lobe.[54] Forty percent of our 35 consecutive patients with extratemporal epilepsy who underwent an operation had epileptogenic foci involving frontal lobe.

The surgical treatment of frontal lobe epilepsy in our experience and in prior reports[16,17,28,55] is less successful than the treatment of either temporal lobe epilepsy or widespread epileptogenic foci requiring hemispherectomy or hemicorticectomy. Nevertheless, 64% of our patients with frontal lobe seizures were significantly improved by surgery. In particular, surgery was successful when radiologic abnormalities corresponded to the seizure focus.

Extensive Hemispheric Abnormality

These cases had the lowest percentage of significantly improved individuals among the anatomically defined categories. Only 46% (6/13) of patients with multilobar resections experienced significant improvement in the control of their seizures. In contrast, our experience with hemicorticectomy (not included in this report) has been much more gratifying. Although some clinical and pathologic differences exist between those who underwent multilobar resection and those who had undergone a hemispheral cortical resection, this observation suggests that the outcome is improved when an extensive surrounding area of cortex can be removed along with the identified epileptogenic tissue. This notion concerning the extent of resection in patients with large hemispheral lesions is consistent with Rasmussen's observation[16] and analogous to the impressions of Van Buren et al[50] on temporal lobe surgery, ie, that limited resection results in less satisfactory control of seizures.

Pathology

Differences in the distribution of pathologic findings between our group of patients and other series of patients with surgically treated epilepsy are not easily explained; however, it is clear that they represent quite dissimilar populations. Bias, whether introduced by patients (families), referring physicians, neurologists, or neurosurgeons, affects the selection of patients for surgery and hence the types of pathologic findings represented. As an alternative, it is interesting to speculate that the underlying processes causing chronic partial epilepsy may have changed over time.

The high proportion of our patients with tumors (34% of the total) is noteworthy and surprising. Our patients with tumor had chronic epilepsy for as long as 25 years (mean, 7.7 years) and, as in other series of surgically treated epilepsy,[16,56,57] the convulsive disorder, not progressive neurologic deficit or intracranial hypertension, was the primary operative indication. While the Montreal, Quebec, Oxford, England, and other groups reported tumors in close to 20% of their patients with intractable seizures,[16,27,54,57] the incidence of neoplasia was much lower in earlier pediatric series.[11,52] Nevertheless, more recent series of operatively treated epilepsy have included a somewhat larger proportion of neoplasms.[58,59] Goldring et al[60] observed that low-grade gliomas detected by CT are a frequent cause of chronic seizure disorders. Although Rasmussen[4,61] reported a high likelihood of tumor in children who came to surgery with intractable epilepsy, the opposite is reported in other pediatric series.[62,63] It is possible that slowly growing and otherwise asymptomatic brain tumors may be a more frequent cause of protracted seizure disorders in children than in adults.

Our patients with nonneoplastic pathologic findings were also significantly different from those described in other articles. Although reports on the incidence of cicatrix as a cause of intractable seizures have ranged from 4% to 20%,[16,29,52] we found only one among 35 consecutive patients who underwent surgery.

Our limited experience with chronic encephalitis (two patients) was disheartening; surgery brought no benefit. The outcome was also poor in two other patients with epilepsia partialis continua who may have had encephalitis but whose histologic features warranted only a "nonspecific" classification. Although others have published similar results in encephalitis,[64] more encouraging surgical outcomes have been reported also.[49,50,63] Of such cases, 15% to 30% may be cured,[51,52,65] especially if the surgical resection is extensive (eg, hemispherectomy) and done after progression of the encephalitic process has ceased, which was not true in our cases.[56,66]

Timing of Surgery

There would seem to be considerable advantage, in terms of limiting human suffering, by controlling seizures as early in life as possible. No inherent reason exists to delay surgery for seizures in patients who meet reasonable criteria. A long latency between the onset of epilepsy and surgery may predispose to poorer postoperative seizure control, particularly when the underlying pathologic process is neoplasia. The observations, albeit on few patients, that those with greater preoperative duration of seizures tended to have poorer results suggest that the duration of extratemporal partial seizures may influence the outcome from surgery; consequently, an earlier operation may lead to better results. This interpretation is consistent with the concept of kindling and secondary epileptogenesis.[67,68] A series that is very much larger would be necessary to definitively answer this question. The high incidence of unsuspected tumors in refractory partial epilepsy of childhood is another reason to favor early surgery; results should be more favorable in patients with neoplasia if the operation is performed at a time when the neoplasm is smaller or, perhaps, less anaplastic. However, when the underlying pathologic process is a smoldering inflamation, early surgical intervention is likely to be unsuccessful[56,66]; outcome is also unfavorable in patients with nonspecific pathologic processes, probably because the abnormality extends beyond the limits of the resection.

In retrospect, we believe that relatively few of our cases were operated on at the optimal age; surgery was delayed in most patients much longer than necessary. The fact that results were usually satisfactory in our patients who underwent surgery beyond adolescence means that there were probably years of needless suffering from epilepsy and the effects of antiepileptic medications. Paradoxically, patients with anatomically well-defined and nonprogressive lesions (eg, vascular malformations) often had the longest delay between onset of seizures and surgery. It seems reasonable to believe that these patients, usually free of seizures after surgery and free of neurologic deficits before and after surgery, would have benefited greatly from earlier intervention.

References

1. Horsley V. Brain-surgery. *BMJ.* 1886;2:670-675.

2. Taylor DC. One hundred years of epilepsy surgery: Sir Victor Horsley's contribution. *J Neurol Neurosurg Psychiatry.* 1986;49:485-488.

3. Gumnit RJ. Postscript: Who should be referred for surgery? In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:71-74.

4. Rasmussen T. Surgical aspects of the treatment of epilepsy. In: *Topics in Child Neurology.* New York, NY: Spectrum Books; 1977:143-157.

5. Aicardi J. General principles of treatment. In: *Epilepsy in Children.* New York, NY: Raven Press; 1986:339.

6. Goldring S. Surgical management of epilepsy in children. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:445-464.

7. Lindsay J, Glaser G, Richards P, Ounsted C. Developmental aspects of focal epilepsies of childhood treated by neurosurgery. *Dev Med Child Neurol.* 1984;26:574-587.

8. Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987.

9. Falconer MA. Significance of surgery for temporal lobe epilepsy in childhood and adolescence. *J Neurosurg.* 1970;33:233-252.

10. Lindsay J, Ounsted C, Richards P. Long-term outcome in children with temporal lobe seizures, V: indications and contra-indications for neurosurgery. *Dev Med Child Neurol.* 1984;26:25-32.

11. Davidson S, Falconer MA. Outcome of surgery in 40 children with temporal-lobe epilepsy. *Lancet.* 1975;1:1260-1263.

12. Meyer FB, Marsh WR, Laws ER Jr, Sharbrough FW. Temporal lobectomy in children with epilepsy. *J Neurosurg.* 1986;64:371-376.

13. Spencer SS. Depth electroencephalography in selection of refractory epilepsy for surgery. *Ann Neurol.* 1981;9:207-214.

14. Green JR, Sidell AD. Neurosurgical aspects of epilepsy in children and adolescents. In: Youmans JR, ed. *Neurological Surgery.* Philadelphia, Pa: WB Saunders Co; 1981;3:3858-3909.

15. Rasmussen T. Commentary: extratemporal cortical excisions and hemispherectomy. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987;417-424.

16. Rasmussen T. Surgery for epilepsy arising in regions other than the temporal and frontal lobes. *Adv Neurol.* 1975;8:207-226.

17. Rasmussen T. Surgery of frontal lobe epilepsy. *Adv Neurol.* 1975;8:197-205.

18. Lombroso CT, Erba G. Primary and secondary bilateral synchrony in epilepsy. *Arch Neurol.* 1970;22:321-334.

19. Lombroso CT. Treatment of status epilepticus with diazepam. *Neurology.* 1965;16:629-634.

20. Wilder B. Electroencephalogram activation in medically intractable epileptic patients: activation technique including surgical follow-up. *Arch Neurol.* 1971;25:415-426.

21. Jones-Gotman M. Psychological evaluation—testing hippocampal function. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:203-211.

22. Milner B. Psychological aspect of focal epilepsy and its neurosurgical management. *Adv Neurol.* 1975;8:299-321.

23. Rausch R. Psychological evaluation. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:181-195.

24. Wada J, Rasmussen T. Intracarotid injection of sodium amytal for the lateralization of cerebral speech dominance: experimental and clinical observations. *J Neurosurg.* 1960;17:266-282.

25. Welch K, Naheedy MH, Abroms IF, Strand RD. Computed tomography of Sturge-Weber syndrome in infants. *J Comp Assist Tomogr.* 1980; 4:33-36.

26. Bhatia R, Kollevold T. A follow-up study of 91 patients operated on for focal epilepsy. *Epilepsia.* 1976;17:61-66.

27. Hahn JF, Sellers M. Surgical techniques for relief from seizures. *Cleve Clin Q.* 1984;51:307-311.

28. Bonis A. Long-term results of cortical excisions based on stereotactic investigations in severe drug resistant epilepsies. *Acta Neurochir.* 1980;30[suppl]:55-66.

29. Goldring S, Gregorie EM. Surgical management of epilepsy using epidural recordings to localize the seizure focus. *J Neurosurg.* 1984;60:457-466.

30. Olivier A, Gloor P, Quesney LF, Andermann F. The indications for and the role of depth electrode recording in epilepsy. *Appl Neurophysiol.* 1983;46:33-36.

31. Talairach J, Banchaud J, Szikla G, Bonis A, Geier S, Vedrenne C. Approche nouvelle de la neurochirurgie de l'épilepsie: méthodologie stéréotaxique et résultats thérapeutiques. *Neurochirurgie.* 1974;20(suppl 1):1-240.

32. Wyler AR, Ojemann GA, Lettich E, Ward AA. Subdural strip electrodes for localizing epileptogenic foci. *J Neurosurg.* 1984;60:1195-1200.

33. Van Buren JM. Complications of surgical procedures in the diagnosis and treatment of epilepsy. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:465-475.

34. Cahan LD, Sutherling W, McCullough MA, Rausch R, Engel E Jr, Crandall PH. Review of the 20-year UCLA experience with surgery for epilepsy. *Cleve Clin Q.* 1984;51:313-318.

35. Erba G, Gobbi G, Burchfiel J, Maister B. Analysis of ictal events recorded on surface and sphenoidal EEG in well-defined hemispheric lesions. *Epilepsia.* 1987;28:585. Abstract.

36. Risinger MW, Engel J Jr, Van Ness PC, Henry TR, Crandall PH. Ictal localization of temporal lobe seizures with scalp/sphenoidal recordings. *Neurology.* 1989;39:1288-1293.

37. Maister B, Erba G, Lombroso CT. The predictive value of interictal background changes and spikes in serial routine EEGs prior to temporal lobectomy. *Epilepsia.* 1987;28:610-611.

38. Ojemann GA, Engel J Jr. Acute and chronic intracranial recording and stimulation. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:263-288.

39. Gloor P. Commentary: approaches to localization of the epileptogenic lesion. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:97-100.

40. Adams CBT, Anslow P, Molyneux A, Oxbury J. Radiological detection of surgically treatable pathology. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:213-233.

41. Ojemann GA. Neurosurgical management of epilepsy: a personal perspective in 1983. *Appl Neurophysiol.* 1983;46:11-18.

42. Oakley J, Ojemann GA, Ojemann LM, Cromwell I. Identifying epileptic foci on contrast enhanced computerized tomographic scans. *Arch Neurol.* 1979;36:669-671.

43. Rich KM, Goldring S, Gado M. Computed tomography in chronic seizure disorder caused by glioma. *Arch Neurol.* 1985;42:26-27.

44. Engel J Jr, Brown WJ, Kuhl DE, Philps ME, Iotta JC, Crandall PH. Pathological findings underlying focal temporal lobe hypometabolism in partial epilepsy. *Ann Neurol.* 1982;12:518-528.

45. Engel J Jr. The use of positron emission tomographic scanning in epilepsy. *Ann Neurol.* 1984;15[suppl]:S180-S191.

46. Theodore WH, Brooks R, Sato S, et al. The role of positron emission tomography in the evaluation of seizure disorders. *Ann Neurol.* 1984; 15[suppl]:S176-S179.

47. Rasmussen T. The place of surgery in the treatment of epilepsy. In: Morley TP, ed. *Current Controversies in Neurosurgery.* Philadelphia, Pa: WB Saunders Co; 1976:463-477.

48. Rossi GF. Considerations on the principles of surgical treatment of partial epilepsy. *Brain Res.* 1975;95:395-402.

49. Morris HH, Luders H, Hahn JF, Lesser RP, Dinner DS, Estes ML. Neurophysiological techniques as an aid to surgical treatment of primary brain tumors. *Ann Neurol.* 1986;19:559-567.

50. Van Buren JM, Ajmone-Marsan C, Matsuga N, Sadowsky D. Surgery of temporal lobe epilepsy. *Adv Neurol.* 1975;8:155-196.

51. Goldring S. A method for surgical management of focal epilepsy, especially as it relates to children. *J Neurosurg.* 1978;49:344-356.

52. Green JR. Percival Bailey Oration: Surgical treatment of epilepsy during childhood and adolescence. *Surg Neurol.* 1977;8:71-80.

53. Green JR, Pootrakul A. Surgical aspects of the treatment of epilepsy during childhood and adolescence. *Ariz Med.* 1982;39:35-38.

54. Mathieson G. Pathologic aspects of epilepsy with special reference to the surgical pathology of focal cerebral seizures. *Adv Neurol.* 1975;8:107-138.

55. Rasmussen T. Surgical therapy of frontal lobe epilepsy. *Epilepsia.* 1963;4:181-198.

56. McNaughton FL, Rasmussen T. Criteria for selection of patients for neurosurgical treatment. *Adv Neurol.* 1975;8:37-48.

57. Rasmussen T. Surgery of epilepsy associated with brain tumors. *Adv Neurol.* 1975;8:227-239.

58. Blume WT, Girvin JP, Kaufmann JCE. Childhood brain tumors presenting as chronic uncontrolled focal seizure disorders. *Ann Neurol.* 1982;12:538-541.

59. Yasargil MG, Wieser HG. Selective amygdalohippocampectomy at the University Hospital, Zurich. In: Engel J Jr, ed. *Surgical Treatment of the Epilepsies.* New York, NY: Raven Press; 1987:653-658.

60. Goldring S, Rich KM, Picker S. Experience with gliomas in patients presenting with chronic seizure disorders. *Clin Neurosurg.* 1986;33:15-42.

61. Rasmussen T. Surgical aspects of temporal lobe epilepsy. *Acta Neurochirurg.* 1980;30[suppl]: 13-24.

62. Aicardi J, Murnaghan K, Gandon Y, Baraton J. Efficacité de la tomodensitométrie dans les épilepsies de l'enfant: problèmes posés par son utilisation. *J Neuroradiol.* 1983;10:127-129.

63. Harwood-Nash DC. Computed tomography and seizures in children. *J Neuroradiol.* 1983; 10:130-136.

64. Gupta PC, Rapin I, Houroupian DS, Roy S, Llena JF, Tandon PN. Smoldering encephalitis in children. *Neuropediatrics.* 1984;15:191-197.

65. Rasmussen T, Olzewski J, Lloyd-Smith D. Focal seizures due to chronic localized encephalitis. *Neurology.* 1958;8:435-445.

66. Rasmussen T, McCann W. Clinical studies of patients with focal epilepsy due to 'chronic encephalitis.' *Trans Am Neurol Assoc.* 1968;93:89-94.

67. Engel J Jr, Cahan L. Potential relevance of kindling to human partial epilepsy. In Wada J, ed. *Kindling 3.* New York, NY: Raven Press; 1986:37-54.

68. Morrell F. Secondary epileptogenesis in man. *Arch Neurol.* 1985;42:318-335.

P300 Brain Activity in Seizure Patients Preceding Temporal Lobectomy

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• Event-related potentials were recorded over occipital and parietal scalp from 20 patients suffering from intractable partial complex seizures prior to undergoing a temporal lobectomy. Subjects were presented with language and nonlanguage visual stimuli using a divided-field, "oddball" paradigm. Although behavioral performance (button-press accuracy, reaction time, and running counts) was comparable across all groups (although accuracy was worse for those in the left temporal group), patients showed tremendous variability in both the amplitude and latency of the P300 response. Particularly notable was the observation that more slow wave activity was present among the patients than among the control subjects, and those scheduled for a left temporal resection evinced more amplitude reduction than those scheduled for a right temporal resection. In addition, a number of patients appeared not to show a P300 response at all. These results are discussed in the context of the utility of using noninvasive event-related potential measures to examine both memory impairment and the integrity of the neural structures that mediate memory functioning in certain patient populations.

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The recording of endogenous brain activity as reflected by event-related potentials (ERPs) has provided a useful metric for assessing a variety of cognitive abilities in the human adult.[1] Of the many components that have been studied, the P300 response has received the most attention.[2,3] The P300 is a positive-going wave of the ERP with a latency greater than 250 milliseconds (although it generally occurs between 300 and 600 milliseconds after stimulus onset), is most pronounced at parietal scalp, and is not specific to any one sense modality.[4] Although unanimity on the meaning of the P300 wave is absent, a large body of research suggests that the response indexes some form of explicit or declarative memory, such as a subject's overt attempt to update working memory.[5-6]

Considerable attention has been directed toward the study of the neural structures responsible for generating the P300 response. For example, using noninvasive measures of magnetic activity (superconducting quantum interference device [ie, SQUID]) in neurologically normal individuals, Kaufman and colleagues[7] have reported neuromagnetic correlates of the P300 wave generated in the hippocampus. Similarly, Halgren,[8,9] McCarthy and Wood,[10] McCarthy and colleagues,[11] Stapelton and Halgren,[12] and Wood et al,[13] using indwelling electrodes in epileptic populations, have also reported P300 correlates generated in medial temporal lobe (MTL) structures (the hippocampus in particular), although there is some disagreement as to exactly where in the hippocampus this response originates,[8-13] and whether the hippocampus is the only source of scalp-recorded P300 activity.

If the proposal is correct that the P300 wave reflects a form of explicit or declarative memory that is mediated by MTL structures, this late ERP component should, in principle, have tremendous clinical utility in assessing certain forms of memory impairment, as well as the integrity of the MTL structures that support explicit memory. An example of a population that might profit from such an examination is patients suffering from intractable partial complex seizures. For example, Puce et al[14] reported that 81% of individuals with unilateral temporal lobe epilepsy manifested little, if any, P300 activity ipsilateral to the seizure focus, although prominent P300 activity was evident in most of these same individuals from the nonepileptogenic lobe. These findings were obtained from depth electrodes implanted in the hippocampi and are in agreement with other reports using comparably invasive measures.[9] To date, however, there are no extant studies in which this issue has been examined noninvasively before surgery. In this article, we discuss the findings from a comparable group of patients observed using surface-recorded ERPs before undergoing a temporal lobe resection.

PATIENTS AND METHODS

Twenty patients scheduled for either a left temporal lobectomy (LTL) (n = 10) or a right temporal lobectomy (RTL) (n = 10) served as subjects. Five strongly right-handed normal volunteers served as controls. Informed consent was obtained from

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all subjects after the experimental procedures had been explained. The neuropsychological and medical profiles of the patients are illustrated in Tables 1 and 2. As is seen in Table 1, the amobarbital sodium procedure indicated left hemisphere dominance for language in 19 patients (although three of these had had some right hemisphere language function) and right-hemisphere dominance in one patient (patient 10). All patients underwent surgery after being tested.

Silver chloride electrodes were attached to the scalp with collodion at O_1, O_z, O_2, P_3, P_z, and P_4 according to the International 10/20 System and referenced to linked earlobe electrodes. A ground silver chloride electrode was placed on the forehead. All impedances were less than 5 kΩ. A bipolar electro-oculogram (EOG) was recorded using miniature electrodes placed on the supraorbital ridge and the outer canthus of the right eye. Impedances for the eye electrodes were generally below 5 kΩ.

Both electroencephalographic (EEG) and EOG signals were amplified and filtered (model 125A5, Grass Instruments, Quincy, Mass). For the EEG, gain was set to 100 000, while for the EOG gain was set to 5000. For both EEG and EOG, the band-pass filter was set at 0.1 to 30 Hz, with a 60-Hz notch filter in place. All signals were monitored on-line by a signal averager (Tracor Northern Signal Averager, Northern Scientific Inc, Madison, Wis) configured as a scope, and were digitized on-line every 5 milliseconds (200 Hz) for 1100 milliseconds, beginning 100 milliseconds before the presentation of the stimulus (pre-event baseline).

Subjects were seated in a chair in front of a rear-projection screen. Side panels occluded the subject's peripheral vision, and all testing took place in the dark. Stimuli (see below) were rear projected onto the half-field screen for 100 milliseconds. The interval between trials varied randomly between 500 and 1000 milliseconds.

The stimuli consisted of black-and-white slides of the word *bat* presented in uppercase letters and a set of *Chinese characters*. (The stimuli and experimental design were selected as part of a series of studies attempting to assess the lateralization of language function, an objective that is not central to the data discussed herein. See reference 15.) Each of these stimuli was embedded in a checkerboard matrix containing twenty-two 1-cm checks along the vertical axis and twenty-eight 1-cm checks along the horizontal axis (ie, a 22 × 28-cm array of checks). The density of the two stimuli (in terms of factors such as character width and lines per millimeter) was comparable, and the stimuli were matched for luminance. The word bat and the Chinese characters each subtended approximately 5 degrees 5 minutes when viewed from a distance of 90 cm; the entire slide (ie, including the checkerboard field) subtended 18 degrees 4 minutes horizontally and 13 degrees 30 minutes vertically when viewed from this same distance. The stimuli were presented on a half-field screen with each stimulus aligned with the center fixation point and moving outward left or right.

Table 1.—Background and Neuropsychological Profile of Patients*

Patient No./ Age, y/Sex	Hand Preference	Language Dominance†	Education, y	WAIS (FSIQ)	WMS MQ
Background and Profile					
1/33/F	Mixed	L	9	99	99
2/32/F	R	L	16+	106	106
3/41/F	R	L	12	112	116
4/32/M	R	L	12+	102	101
5/37/F	R	L	16	114	118
6/32/M	R	L	12	93	87
7/54/M	R	L	16	108	118
8/26/M	Bilateral	L, some R	13	80	77
9/23/M	R	L	12	89	83
10/29/M	L	R	12, special education	87	70
11/21/F	R	L	16	117	105
12/29/F	R	L, uncertain R	8‡	93	100
13/48/F	R, bilateral	L, some R	9	84	77
14/32/F	R	L	13	108	116
15/23/F	R	L	14.5	108	112
16/37/M	R	L	13	84	76
17/26/F	R	L	12+	103	100
18/36/M	L/R	L	16	109	91
19/23/M	R	L	12, special education	77	64
20/20/M	R	L	13	84	70
Means (SD) for Patient Groups					
RTL (n = 10) 31 (8.1)	...	...	11.9 (2.7)	101.7 (13.1)	100.9 (14.0)
LTL (n = 10) 30.8 (10.0)	...	...	12.8 (1.5)	94.7 (12.6)	87.7 (19.3)

*WAIS indicates the Wechsler Adult Intelligence Scale; FSIQ, Full Scale Intelligence Quotient; WMS, Wechsler Memory Scale; MQ, Memory Quotient; RTL, right temporal lobectomy; and LTL, left temporal lobectomy.

†In all cases, dominance was determined by the amobarbital sodium procedure.

‡This patient's religious affiliation dictated that public education terminate at grade 8.

Table 2.—Seizure History

Patient No.	Age at Onset, y	Seizure Duration, y	Seizure Focus	Family History
History				
1	11	22	R*	None
2	23	8	R*	None
3	21	20	R†	None
4	1	31	R*	None
8	5	21	R*	None
12	12	27	R†	None
11	18	3	R*	None
13	42	6	R†	Niece
14	20	12	R*	None
15	0.5	22.5	R*	None
5	5	32	L*	None
6	15	17	L†	None
7	53	1	L†	None
9	3	19	L*	None
10	0.5	38	L*	None
16	0.5	36.5	L†	Brother
17	17	9	L*	None
18	10	26	L*	None
20	1	19	L*	None
19	1	22	L*	None
Means (SD) for Patient Groups				
Right temporal lobectomy (n = 10)	12.4 (10.6)	18.6 (9.2)	...	...
Left temporal lobectomy (n = 10)	10.4 (14.6)	20.7 (9.6)	...	...

*Determined by noninvasive measures (eg, electroencephalogram).

†Determined by grid or depth recording.

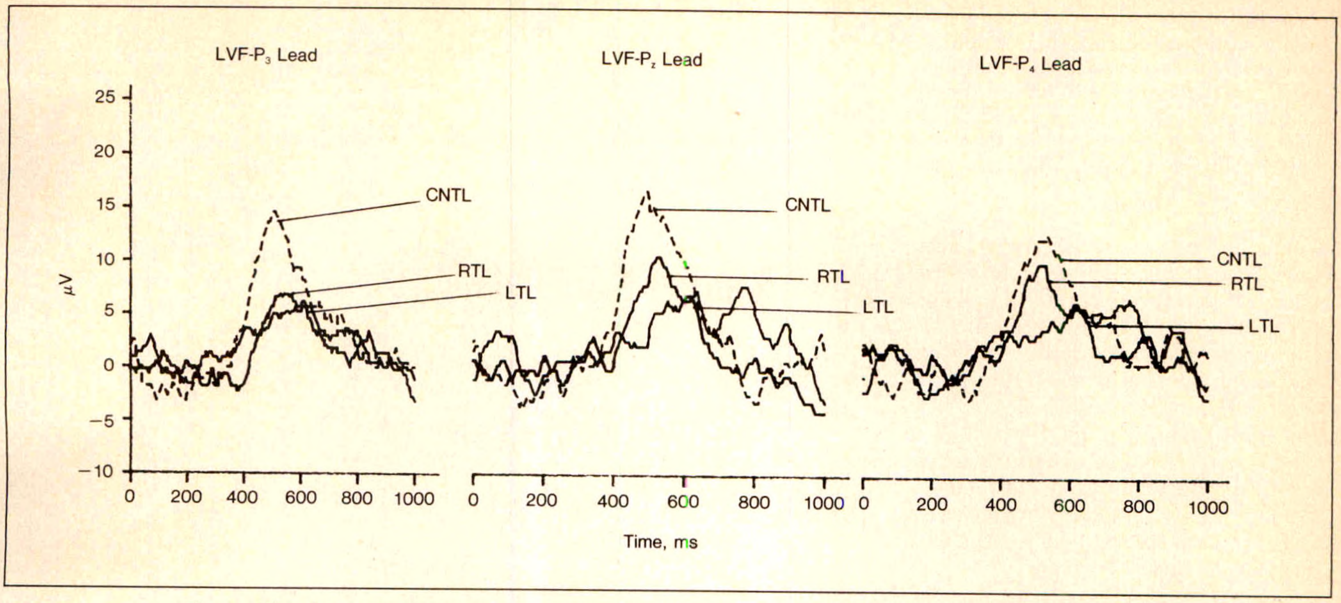

Fig 1.—Grand-average difference waveforms (80% nontarget subtracted from 20% target) for control subjects (CNTL) (dashed line), those who underwent a left temporal lobectomy (LTL) (light solid line), and those who underwent a right temporal lobectomy (RTL) (dark solid line) to left visual field (LVF) presentations of the word *bat* for left parietal (P$_3$), midline (P$_z$), and right parietal (P$_4$) leads. The grand average was computed by averaging each subject's average response (n = 5 for control subjects and n = 10 for each of the two patient groups). Note ordering of P300 amplitude, with control subjects showing most amplitude followed by those who underwent an RTL and then those who underwent an LTL. Positive is up.

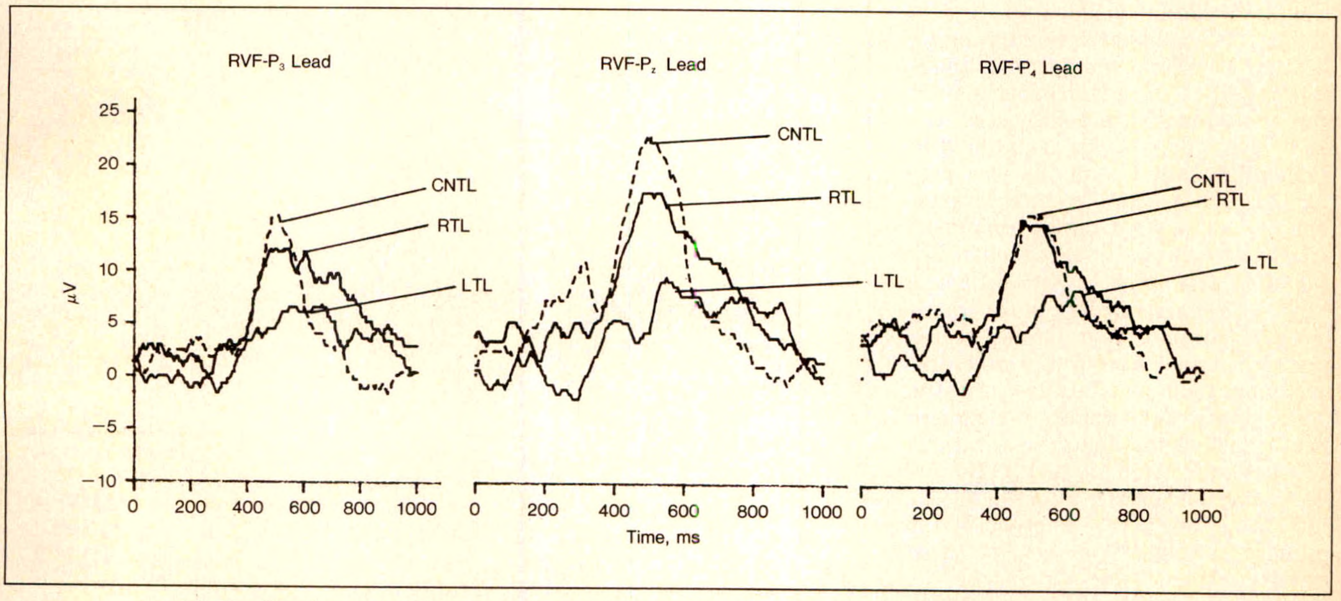

Fig 2.—Grand-average difference waveforms (80% nontarget subtracted from 20% target) for control subjects (CNTL) (dashed line), those who underwent a left temporal lobectomy (LTL) (light solid line), and those who underwent a right temporal lobectomy (RTL) (dark solid line) to right visual field (RVF) presentations of the word *bat* for left parietal (P$_3$), midline (P$_z$), and right parietal (P$_4$) leads. The grand average was computed by averaging each subject's average response (n = 5 for control subjects and n = 10 for each of the two patient groups). Note ordering of P300 amplitude, with control subjects showing most amplitude followed by those who underwent an RTL and then those who underwent an LTL. Positive is up.

Subjects were tested with the two stimuli paired in a simple 20%-80% "oddball" task. Each stimulus served as a target (random 20% occurrence) and as a nontarget (80% occurrence) event separately within two trial blocks of 200 trials each. Subjects received four such trial blocks, two of which involved stimulating the right visual field and two of which involved stimulating the left visual field, producing a total of 800 trials presented to each subject. The order of presentation was counterbalanced across subjects. Subjects were asked to push a button, using their preferred hand, whenever a target appeared; they were also asked to keep a running count of the targets. At the end of each condition, the patient reported this count to the experimenter.

Artifact Rejection

Any trial that contained an EOG signal that exceeded 25 µV resulted in rejecting the entire trial from subsequent analysis.

Any EEG signal that exceeded analog-to-digital values for more than 50 milliseconds at a given lead resulted in rejecting the data from that lead; if artifacts occurred at more than two leads, the entire trial was rejected. In this manner, only artifact-free data were used in the final data analysis.

RESULTS

The findings of the control subjects have been reported in detail elsewhere[15]; therefore, these data will only be abstracted here. In addition, although a stimulus factor (ie, the word bat vs the Chinese characters) was entered into most statistical analyses, the discussion will be restricted to when the word bat served as the target event, as discrimination between patient groups was always stronger for this stimulus than it was for the Chinese characters.

Summary of Control Subjects' Performance

In brief, the analysis of the control subjects' behavioral data revealed that running counts of target presentations (n = 40 in each condition) were nearly perfect, as was button-press accuracy ($M = 39.8$ and 39.4 for the right visual field and the left visual field, respectively). As would be expected, running counts, accuracy, and reaction times did not differ across the experimental manipulation (eg, accuracy was the same regardless of the visual field to which the target stimulus was presented). With regard to the ERP data, control subjects evinced prominent P300 activity to all target events. Restricting discussion to parietal leads, where P300 activity was most prominent, the amplitude difference scores for right-handed subjects were larger and more strongly lateralized over the left, language-dominant hemisphere for right visual field presentations (10.8 μV at P_3 vs 8.0 μV at P_4) than for left visual field presentations (8.6 μV at P_3 vs 7.4 μV at P_4). (See reference 15 for a more complete discussion of these results.)

Patient-Subjects' Performance

Behavioral Performance.—Patients' running counts were generally accurate across all conditions. Data analysis was, therefore, restricted to button-press accuracy and the resulting reaction times.

Button Press Accuracy.—A Group (LTL or RTL) × Visual Field (left or right) × Stimulus (the word bat or the Chinese characters) repeated-measures analysis of variance (ANOVA) was computed on button-press accuracy. This analysis revealed a significant interaction between group, visual field, and stimulus ($F = 7.14$ [1,18], $P < .02$). Specific follow-up tests (the Newman-Keuls procedure for Student's t test) revealed that the two patient groups did not differ from one another in their responses to the word bat presented in the right visual field ($M = 37.4$ and 37.3 for right and left temporal lobe groups, respectively). However, those in the left temporal lobe group performed significantly worse than did those in the right temporal lobe group in their responses to the word bat presented in the left visual field ($M = 40.0$ and 35.1 for right and left temporal lobe groups, respectively).

Reaction Time.—Mean reaction

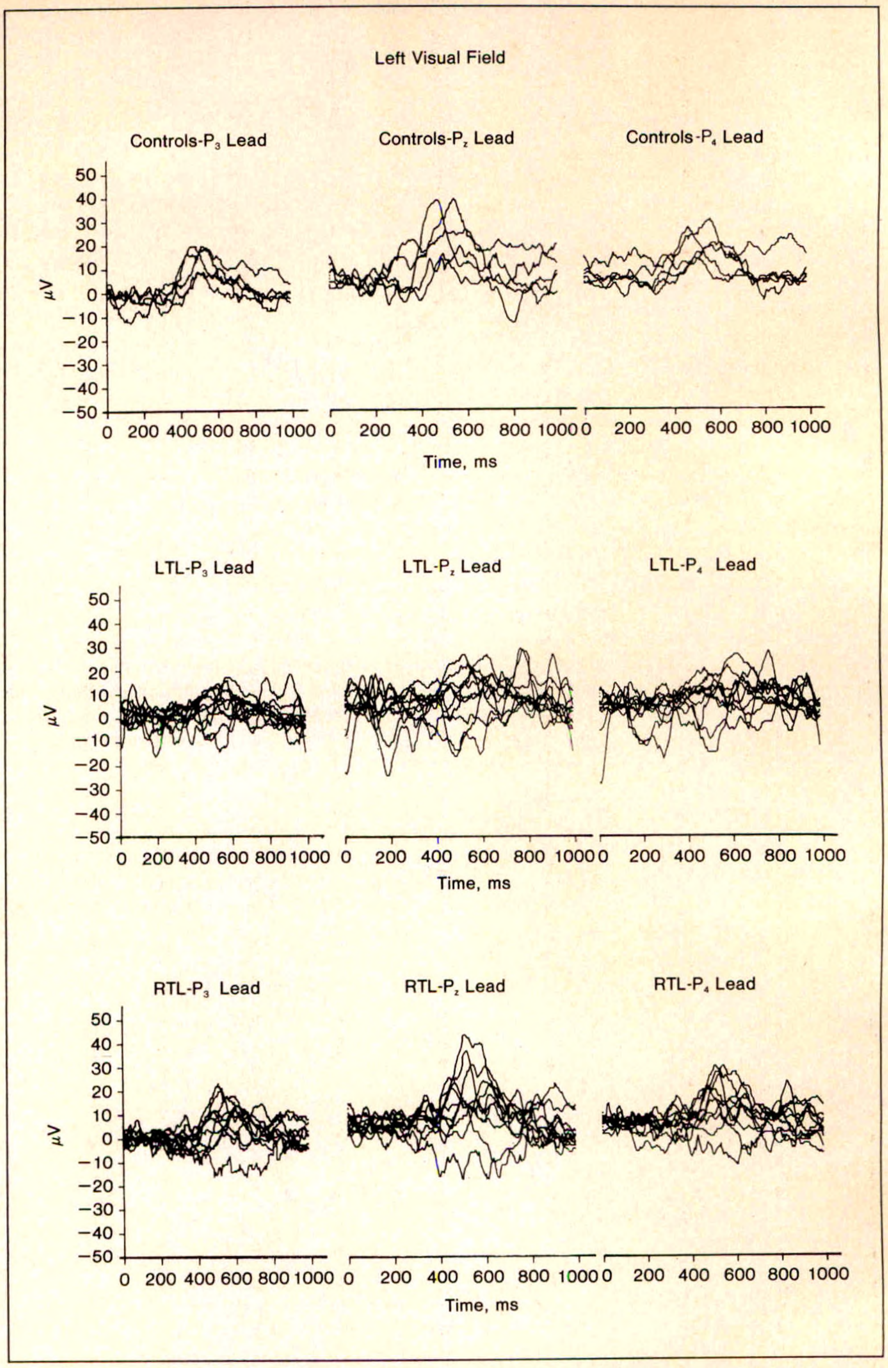

Fig 3.—Superimposition of each subject's average against all other subjects' averages for control subjects (top panel), those who underwent a left temporal lobectomy (LTL) (middle panel), and those who underwent a right temporal lobectomy (RTL) (bottom panel) to left visual field presentations of the word *bat* for left parietal (P_3), midline (P_z), and right parietal (P_4) leads. Each average was computed by averaging all artifact-free trials. The data displayed are for the five control subjects and for the 10 LTL and 10 RTL patients. Positive is up.

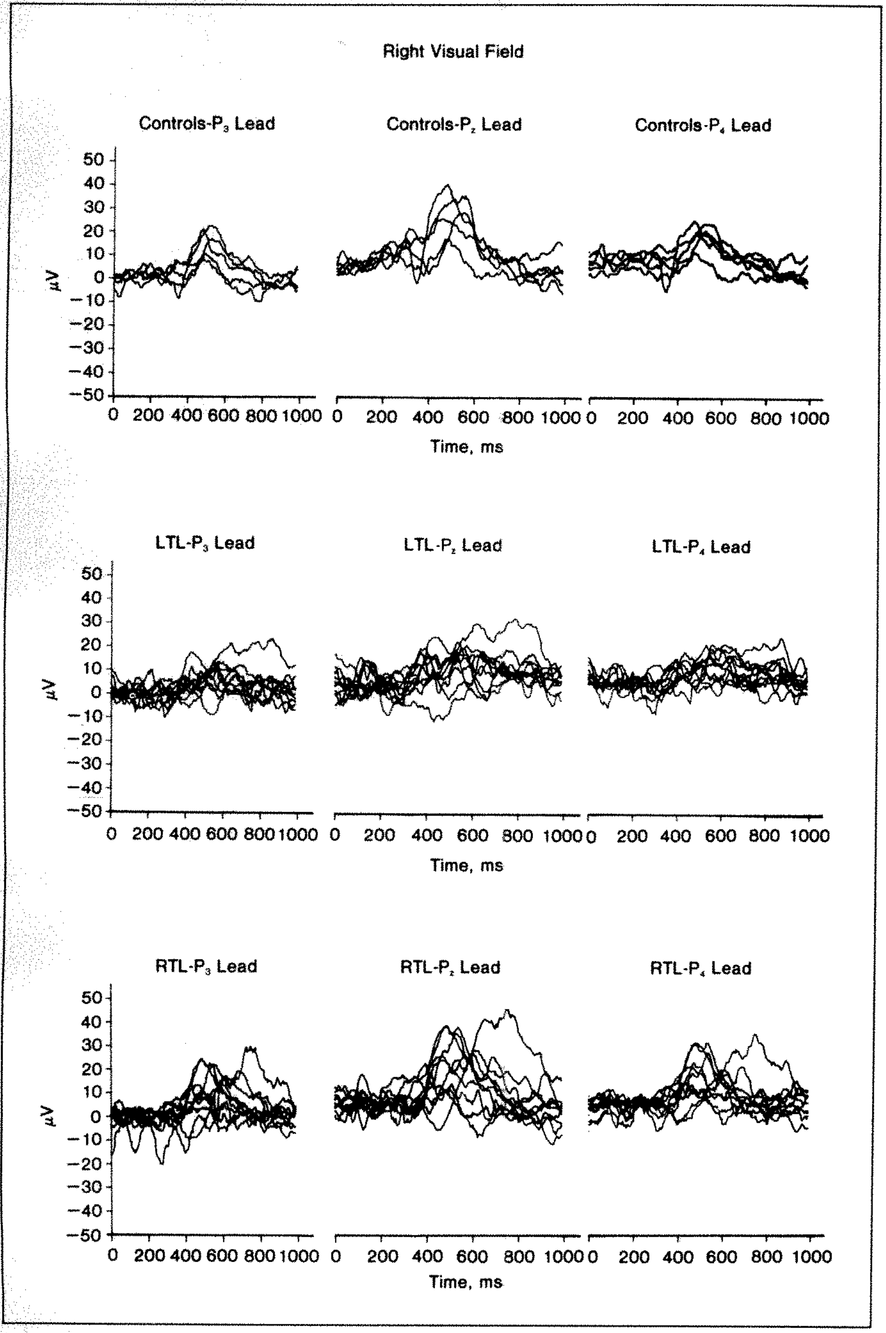

Fig 4.—Superimposition of each subject's average against all other subjects' averages for control subjects (top), those who underwent a left temporal lobectomy (LTL) (middle), and those who underwent a right temporal lobectomy (RTL) (bottom) to right visual field presentations of the word *bat* for left parietal (P_3), midline (P_z), and right parietal (P_4) leads. Each average was computed by averaging all artifact-free trials. The data displayed are for the five control subjects and for the 10 LTL and 10 RTL patients. Positive is up.

times for the word bat to both visual fields for the two patient groups and the control group ranged from 588 to 601 milliseconds; a repeated-measures ANOVA computed on reaction times identical to those computed on button-press accuracy revealed no significant differences between the two patient groups.

ERP Analyses.—Difference waveforms were computed via point-by-point subtraction of average nontarget from average target waveforms in each condition (Figs 1 through 4). The grand-average difference waveforms at parietal leads for patient and control subjects can be seen in Figs 1 and 2; Figs 3 and 4 present each subject's average waveform superimposed on the average waveforms of all other subjects in the group.

Inspection of Figs 1 and 2 reveals that the patients' grand-average difference waveforms are more irregular and less sharply peaked than are those of the control subjects. Reduced amplitude in the P300 latency range is also evident, particularly for the LTL patients. However, the most notable differences between the patient and control groups can be seen in Figs 3 and 4. Here, it is evident that the difference waveforms are considerably more variable among the patients than they are among the control subjects in terms of both the clarity and the latency of P300 peak amplitudes; overall, LTL waveforms appear to be more clearly deviant from control waveforms, especially with right visual field presentations (Fig 4).

Because many patients' ERPs contained slow-wave activity rather than peaked components, areas were integrated relative to the prestimulus baseline for amplitude deflections in the interval between 300 and 1000 milliseconds. These areas were calculated separately on target and nontarget ERPs within each experimental condition, and statistical analyses were performed on difference scores computed by subtraction of nontarget areas from target areas. A Group (LTL or RTL) × Visual Field (left or right) × Stimulus (the word bat or the Chinese characters) × Lead (O_z and P_z) repeated-measures ANOVA of these area difference scores revealed a significant interaction between visual field and group for the midline leads (F = 5.61 [1,18], $P < .05$). An identical ANOVA for the lateral leads (O_1, O_2, P_3, and P_4) revealed a somewhat smaller effect for the same interaction (F = 3.70 [1,18], $P < .07$). Specific follow-up tests (the Newman-Keuls procedure for Student's *t* test) revealed that right visual field presentations of the word bat invoked much larger P300 area-difference scores at parietal leads for the RTL group than for the LTL group; in contrast, RTL responses decreased during left visual field presentations of the word bat while LTL responses increased slightly. These findings are illustrated in Table 3 and in Fig 5.

Statistical analysis of both patient and control ERPs was not conducted, because ANOVAs have little power to detect differences when groups are relatively small and unequal in size, as in this study. However, when patients' area-difference scores were inspected relative to those of the control subjects, the trend across lateral parietal leads was for right visual field presen-

Table 3.—Mean ERP Area Difference Scores*

	Left Visual Field		Right Visual Field	
Lead	LTL	RTL	LTL	RTL
O_1	86 (1182)	500 (1546)	1083 (2167)	2315 (3176)
O_z	768 (1045)	417 (2231)	698 (1488)	1860 (2619)
O_2	515 (1524)	531 (1505)	227 (1263)	2205 (3203)
P_3	1728 (3883)	1613 (2401)	1637 (2149)	3667 (3821)
P_z	2534 (2426)	1569 (3261)	2254 (1993)	4101 (4136)
P_4	1241 (2136)	1411 (3254)	1422 (850)	3010 (3674)

*Event-related potentials (ERP) areas were integrated relative to prestimulus baseline for sustained amplitude deflections in the interval from 300 to 1000 milliseconds. See text for computation of difference scores. Means are displayed only for blocks of trials in which the word *bat* was the target stimulus. Standard deviations are in parentheses. LTL indicates left temporal lobectomy; RTL, right temporal lobectomy.

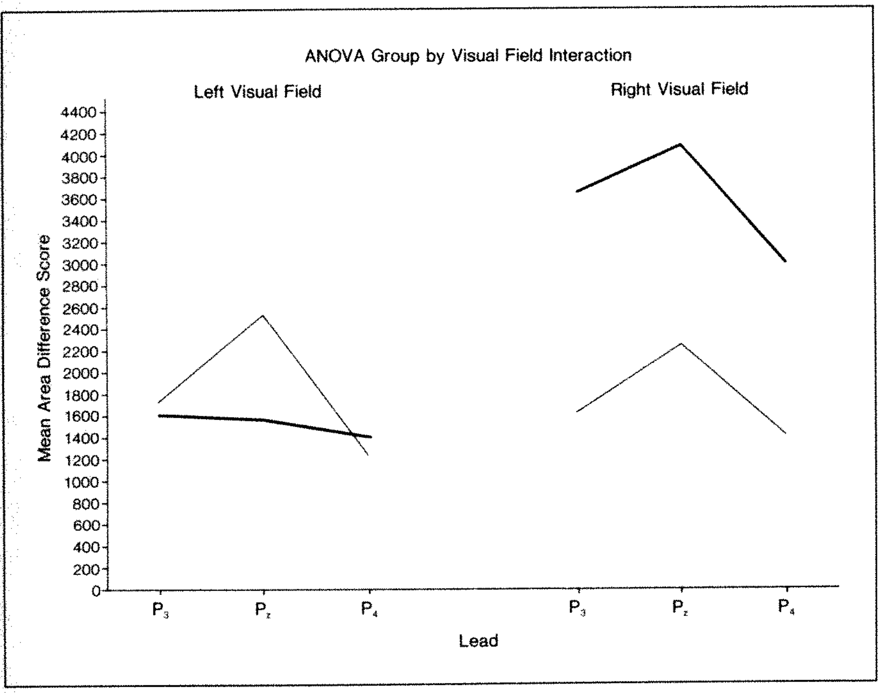

Fig 5.—Illustration of mean area difference scores for Group (right temporal lobectomy [RTL] or left temporal lobectomy [LTL]) × Visual Field (right or left) interaction reported in text. The thick line represents the responses of patients scheduled for an RTL, while the thin line represents the responses of patients scheduled for an LTL. ANOVA indicates analysis of variance.

tations of the word bat to invoke the greatest area-difference score for the RTL group, followed by the control subjects (46% smaller than RTL group) and then the LTL group (67% smaller than RTL group). With left visual field presentations of the word bat, area-difference scores for the RTL and control groups were both reduced relative to right visual field presentations of the word (44% and 4% smaller, respectively); however, the LTL group scores increased (30% larger).

Relation Between Patients' ERPs and Verbal Memory Neuropsychological Profile.—An examination of patients' Wechsler Memory Scale scores suggested that memory impairment was reflected by two different ERP manifestations, and that these occurred primarily when stimuli were delivered to the affected hemisphere of each patient. Specifically, verbal memory impairment in the LTL group was related to decreased P300 area, as indicated by moderate positive correlations of activity at the left parietal lead during right visual field presentations with immediate and delayed Logical Memory scores (.41 and .35 for immediate vs delayed recall, respectively). In contrast, verbal memory impairment in the RTL group was related to increased P300 area, primarily in the form of diffuse slow-wave activity in target waveforms, as indicated by negative correlations of parietal activity during left visual field presentations with the same Logical Memory recall scores (−.52 and −.63 for immediate and delayed recall, respectively). In this context, one RTL case can be seen in Fig 3 as an outlier with markedly delayed, predominantly slow-wave activity only when the word bat was presented in the right visual field. This RTL patient (excluded from the correlations above) demonstrated significant verbal memory impairment on the Wechsler Memory Scale as well as partial right hemisphere language representation on the amobarbital sodium procedure.

COMMENT

Unlike the control subjects, patients did not display significant patterns of lateralized scalp P300 activity in response to the right vs left visual field presentations of a verbal stimulus, despite the fact that 19 of 20 patients were left hemisphere dominant for language (as, presumably, were the right-handed control subjects). Instead, a less precise effect of visual field alone was observed in that RTL patients displayed greater P300 activity across all parietal leads in response to right visual field stimulus presentations. Such findings are not surprising, considering the morphological differences in the P300 activity recorded in the patients relative to the control subjects. Although most RTL patients displayed a "control-like" P300 peak in response to half-field presentations of a verbal stimulus, this deflection contained considerable overlapping slow-wave activity as well. Moreover, LTL patients displayed an irregular waveshape and a general reduction in P300 area that was most noticeable when the word bat was presented to the left (dominant) hemisphere. The relatively slower and more irregular ERP activity of the patients apparently impeded localization of verbal memory effects in terms of scalp topography, since such localization was achieved using the clearly defined P300 peaks of control subjects.[15]

Aberrant P300 activity among our LTL patients is consistent with reports of P300 reduction, measured intracranially, ipsilateral to seizure focus,[11,14,16] although the current scalp-recorded effects depended on half-field stimulus presentations rather than electrode recording sites. The restriction of P300 amplitude reduction to LTL patients only is also consistent with their relatively greater neuropsychological impairment (Table 1) and the verbal content of the oddball task. Presumably, RTL patients would have demonstrated reduction in P300 amplitude if a purely abstract (unnameable) spatial stimulus had been employed, as compared with the Chinese characters serving as a linguistic control stimulus in the current study.

The scalp-recorded effects for the LTL group are quite comparable with those noted by Puce et al,[14] who recorded P300 activity in patients using indwelling electrodes. In this context, our findings are encouraging in two respects. First, additional support is now provided for the proposition that measurement of P300 activity can be used to assess the integrity of the neural structures that underlie explicit memory. Second, it appears that this assessment can be accomplished noninvasively, provided that appropriate experimental manipulations are employed, such as half-field presentation of verbal and nonverbal material. A more clinically relevant extension of the methodology in this study would be to employ a more complex task using verbal and nonverbal stimuli from neuropsychological tests with demonstrated sensitivity to lateralized or "material-specific" memory processes. For example, one could pretest patients with lists of words and unnameable shapes from short-term memory tasks (eg, the Logical Memory and Visual Reproduction subtests of the Wechsler Memory Scale) and then conduct ERP testing in which patients are required to discriminate half-field presentations of previously unencountered words and shapes from those encoded during pretesting.

Although this report is, to the best of our knowledge, the first to describe P300 activity recorded noninvasively in patients with temporal lobe partial seizures prior to surgery, note that similar work has been done with patients many years after they underwent a temporal lobectomy. In this line of investigation, Johnson[17-19] has reported that P300 amplitude and latency in individuals who had undergone unilateral resection of the temporal lobe (including the pes, uncus, amygdala, and the anterior portion of the hippocampal complex) were similar to those of normal control subjects. The current results suggest that P300 morphologic activity is considerably more irregular and variable in patients prior to undergoing a temporal lobectomy than it is in neurologically intact individuals. Furthermore, our results suggest that memory impairment may be manifested in various alterations of ERP morphology, which are generated by the interaction of a patient's specific underlying neural dysfunction with the specific nature of the memory task imposed. Both preoperative and postoperative testing, therefore, appears to be necessary before inferences can be drawn regarding memory functions and generators of scalp-recorded ERP components in epileptic populations.

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References

1. Donchin E. *Cognitive Psychophysiology.* Hilldale, NJ: Lawrence Erlbaum Assoc Inc; 1984.
2. Johnson R Jr. The amplitude of the P300 component of the event-related potential: review and synthesis. In: Ackles PK, Jennings JR, Coles MGH, eds. *Advances in Psychophysiology.* Greenwich, Conn: JAI Press Inc; 1988:69-138.
3. Pritchard WS. Psychophysiology of P300. *Psychol Bull.* 1981;89:506-540.
4. Fabiani M, Gratton G, Karis D, Donchin E. The definition, identification, and reliability of measurement of the P300 component of the event-related potential. In: Ackles PK, Jennings JR, Coles MGH, eds. *Advances in Psychophysiology.* Greenwich, Conn. JAI Press Inc; 1987.
5. Donchin E, Coles MGH. Is the P300 component a manifestation of context updating? *Behav Brain Sci.* 1988;11:357-374.
6. Verleger R. Event-related potentials and cognition: a critique of the context updating hypothesis and an alternative interpretation of P_3. *Behav Brain Sci.* 1988;11:343-356.
7. Okada YC, Kaufman L, Williamson SJ. The hippocampal formation as a source of the slow endogenous potential. *Electroencephalogr Clin Neurophysiol.* 1983;55:417-426.
8. Halgren E. Human hippocampal and amygdala recording and stimulation: evidence for a neural model of recent memory. In: Squire LR, Butters N, eds. *Neuropsychology of Memory.* New York, NY: Guilford Press; 1984;165-182.
9. Halgren E. The P_3: a view from the brain. *Behav Brain Sci.* 1988;11:357-374.
10. McCarthy G, Wood CC. Intracranial recordings of endogenous ERPs in humans. In: Ellingson RJ, Murray NMF, Halliday AM, eds. *The London Symposium (EEG Supplement 39).* Amsterdam, the Netherlands: Elsevier Science Publishers; 1987.
11. McCarthy G, Darcey TM, Wood CC, Williamson PD, Spencer DD. Asymmetries in scalp and intracranial endogenous ERPs in patients with complex partial epilepsy. In: Engel J, Ojemann G, Luders H, Williamson PD, eds. *Fundamental Mechanisms of Human Brain Function.* New York, NY: Raven Press; 1987:51-59.
12. Stapleton JM, Halgren E. Endogenous potentials evoked in simple cognitive tasks: depth components and task correlates. *Electroencephalogr Clin Neurophysiol.* 1987;67:44-52.
13. Wood CC, McCarthy G, Squires NK, et al. Anatomical and physiological substrates of event-related potentials: two case studies. *Ann N Y Acad Sci.* 1984;425:681-721.
14. Puce A, Kalnins RM, Berkovic SF, et al. Limbic P_3 potentials, seizure localization, and surgical pathology in temporal lobe epilepsy. *Ann Neurol.* 1989;26:377-385.
15. Nelson CA, Collins PF, Torres F. The lateralization of language comprehension using event-related potentials. *Brain Cogn.* 1990;14:92-112.
16. Meador KJ, Loring DW, Gallagher BB, et al. Limbic evoked potentials predict site of epileptic focus. *Neurology.* 1987;37:494-497.
17. Johnson R Jr. P300 activity in patients following unilateral temporal lobectomy: a preliminary report. In: McCallum WC, Zappoli R, Deneth F, eds. *Cerebral Psychophysiology: Studies in Event-Related Potentials (EEG Supplement 38).* Amsterdam, the Netherlands: Elsevier Science Publishers; 1986.
18. Johnson R Jr. Task-related changes in P300 scalp distribution in temporal lobectomy patients. In: Johnson R Jr, Rohrbaugh JW, Parasuraman R, eds. *Current Trends in Event-Related Potential Research (EEG Supplement 40).* Amsterdam, the Netherlands: Elsevier Science Publishers; 1987.
19. Johnson R Jr. Scalp-recorded P300 activity in patients following unilateral temporal lobectomy. *Brain.* 1988;111:1517-1529.

Cognition-Independent Neurologic Symptoms in Normal Aging and Probable Alzheimer's Disease

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• Deep tendon reflexes, plantar responses, muscle tone, and release signs were studied as 14 individual clinical variables and as five summary variables in 135 aged subjects, including 27 control subjects, 20 subjects with mild cognitive impairment, and 88 subjects with successive stages of probable Alzheimer's disease. Changes in activity of elicited responses were rated on a seven-point scale. Results were analyzed both as prevalence and mean degree of change in activity. Rating on a variable combining all 14 individual variables was significantly higher in a group with mild cognitive impairment than in a control group. Subjects with an early stage of Alzheimer's disease had both higher prevalence of increased activity and increased mean scores of deep tendon reflexes and muscle tone. They had a higher prevalence of increased activity on a variable combining three release signs. Patients with a late stage of Alzheimer's disease had significantly increased prevalence and mean scores of muscle tone and grasping and sucking reflexes compared with control subjects and patients with the early stage of Alzheimer's disease.

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Alzheimer's disease (AD) is an insidious and slowly progressive form of dementia with widespread and characteristic neuropathologic changes.[1-3] In a majority of cases, gross impairment of motor function is not obvious in the early stages of the illness. Ambulation is not seriously impaired until language and other cognitive processes have been severely compromised,[4-6] but in the late stage of the illness it declines rapidly.[5,6]

Changes in deep tendon reflexes, plantar responses, and muscle tone may be early signs of disturbed motor function, but they can also accompany normal aging.[7] Increased muscle tone has been reported as the most common motor abnormality related to increasing severity of dementia in patients with probable AD.[8] Release signs (also referred to as primitive, developmental, or neonatal reflexes, or, alternatively termed, cortical or frontal disinhibition signs) are commonly associated with dementia, but may also occur in healthy elderly individuals.[9-16] They are strongly associated with the severity of dementia.[17]

Reflex testing ranks as the premier objective measure of nervous system integrity.[7] Reflexes can be evaluated throughout the entire course of dementia, including the end stage when cognitive testing results in uniform bottom scores.[18-20] As such, they may be useful as independent markers of disease progression and as indicators of potential therapy.[21]

The existing literature shows considerable variability in reported incidence and significance of specific release signs in dementia. Possible explanations are differences in the stage of dementia during which these signs are elicited, differences in methods or scoring, and inclusion of dementia of various causes.

We report the results of a cross-sectional investigation of deep tendon reflexes, plantar responses, muscle tone, and release signs rated on a seven-point activity scale in a group of 135 elderly subjects. Because it is important to eliminate changes associated with normal aging, we have included a control group of healthy community-residing and well-functioning aged subjects. The study group encompasses the entire range of subjects from healthy normal elderly and mildly cognitively impaired subjects to patients with end-stage AD.

SUBJECTS AND METHODS

Subjects

We studied 135 consecutive community-residing and nursing home-residing elderly persons, including normal elderly control subjects with and without subjective memory impairment ($n = 27$), patients with mild objective cognitive impairment ($n = 20$), and patients with AD in all stages of severity ($n = 88$). All cognitively impaired patients had been living normal lives before the onset of their illness. Their mean educational level was 13.1 years. Informed consent was obtained after the nature of the procedure had been fully explained. All patients with the diagnosis of AD fulfilled the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria for a clinical diagnosis of probable Alzheimer's disease.[22] All subjects underwent neurologic, psychiatric, and physical examinations, as well as a comprehensive neuropsychological test battery, selected for its sensitivity to cognitive deficit in aging and dementia, including tests for evaluation of recent memory, attention, psychomotor speed, language, visuospatial function, and praxis. Also for all subjects, electrocardiograms; routine laboratory tests including thyroid function, serum B_{12} and folate levels; and either computed tomographic or magnetic resonance imaging scans of the brain were performed. Excluded from the study were all individuals with conditions known to adversely affect cognition or functioning, ie, patients with a history of head trauma with resulting neurologic sequelae, history of seizures prior to the onset of AD, Parkinson's disease with its onset prior to the onset of AD, mental retardation, psychosis, or depression, as well as patients with vascular dementia whose Modified Ischemia Scale score was 4 or greater,[23] patients with evidence of Binswanger's disease, and patients

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Table 1.—Subject Characteristics*

	Mean Age, y						
GDS Stage	**n**	**Men**	**n**	**Women**	**N**	**Total**	**Mean MMSE Score**
1 and 2	9	69.7 ± 12.3	18	58.7 ± 7.4	**27**	68.7 ± 12.1	29.0 ± 1.2
3	6	70.8 ± 14.1	14	73.6 ± 6.4	**20**	72.8 ± 9.1	24.9 ± 3.3
4	8	70.6 ± 8.3	25	72.5 ± 7.0	**33**	72.1 ± 7.3	20.1 ± 3.4
5	16	71.6 ± 9.0	15	76.0 ± 8.8	**31**	73.7 ± 9.0	14.7 ± 3.3
6	5	77.7 ± 6.7	12	71.5 ± 8.7	**17**	73.3 ± 8.5	7.3 ± 5.4
7	1	87.6 ± 0.0	6	81.5 ± 5.5	**7**	82.4 ± 5.5	0.0 ± 0.0
Total subjects	**45**	72.0 ± 10.1	**89**	72.9 ± 9.2	**135**	72.6 ± 9.5	18.8 ± 8.6

*Values are mean ± SD. GDS indicates Global Deterioration Scale; MMSE, Mini-Mental State Examination. See "Measures" section for explanation of GDS stages.

with peripheral neuropathy or with significant arthropathy. Table 1 shows the demographic characteristics of subjects at the time of their examination. There were no differences in racial or ethnic makeup in any clinical severity group.

Measures

The severity of cognitive and functional impairment was assessed using the Global Deterioration Scale (GDS)[24] and the Mini-Mental State Examination (MMSE).[25] Table 1 shows the GDS scores with corresponding mean MMSE scores of the study subjects. The GDS stages can be summarized as follows: GDS 1, no subjective complaints of memory deficit and no memory deficit on clinical interview; GDS 2, subjective complaints of memory deficits with no objective deficits in employment or social situations; GDS 3, earliest clear-cut deficit with objective evidence of deficit on detailed interview and decreased performance in demanding employment and social settings; GDS 4, clear-cut deficit on careful clinical interview manifest in such areas as decreased knowledge of current and recent events and concentration deficits on serial subtractions, with decreased ability in performance of complex tasks such as managing finances or preparing dinner for guests; GDS 5, deficit sufficient to interfere with independent community survival, with inability to recall major relevant aspects of current and past life during the clinical interview (eg, address or telephone number of many years or names of certain close family members, or the names of schools attended for years and from which the subjects may have graduated); GDS 6, deficits in daily life activities such as dressing and bathing, with general lack of awareness regarding recent events and life experiences and sketchy knowledge of personal history; and GDS 7, deficit sufficient to require assistance with toileting and feeding, with both urinary and fecal incontinence, with severely circumscribed or entirely absent verbal abilities, and, ultimately, with loss of ambulatory skills. The subject population consisted of 27 control subjects (GDS stages 1 or 2), 20 subjects with mild but objectively demonstrable impairment (GDS stage 3), and 88 subjects with moderate to very severe impairment from probable AD (GDS stages 4 through 7) (Table 1).

Established procedures were used for examination of deep tendon reflexes and plantar responses,[26] muscle tone (ie, paratonic rigidity), and release signs.[27] Four deep tendon reflexes (biceps, triceps, quadriceps, and gastrocnemius-soleus), as well as the plantar responses, presence of paratonic rigidity (also referred to as paratonia and defined as an irregular opposition of the musculature of the limb to passive manipulation), and eight release signs (sucking reflex [tactile and visual], hand and foot grasp, rooting, snout reflex, glabellar blink reflex, and palmomental reflex) were studied. The degree of activity of these reflexes was rated on a seven-point activity scale. On this scale, points 1, 3, 5, and 7 were well-defined points, while points 2, 4, and 6 were intermediate numerical scores, used in situations falling between the four well-defined points.

For the deep tendon reflexes, the criteria for increased activity were any or all of the following: amplitude, briskness, extent of stimulus zone within which a specific reflex could still be elicited, clonus, and/or occurrence of a spinal defense reflex, ie, mass response.[28] Briefly, a rating of 1 denoted a normal or hypoactive response; a rating of 3 indicated a notable increase in amplitude and/or briskness; a rating of 5 denoted a distinct increase in amplitude, briskness, and/or extent of stimulus zone; and a rating of 7 denoted a very prominent, exaggerated response with clonus and/or spread of the activity to neighboring joints or a mass response.

For the plantar response, a rating of 1 denoted plantar flexion of the big toe, a rating of 3 denoted an absence of either dorsiflexion or plantar flexion of the big toe, a rating of 5 indicated a distinct and tonic (unequivocal) dorsiflexion, and a rating of 7 denoted a dorsiflexion of the big toe with spreading of the toes and/or a spinal defense reflex.

Paratonic rigidity, defined as stiffening of a limb in response to contact with the examiner's hand and an involuntary resistance to passive changes in position and posture, was graded according to the amount of passive force necessary to elicit it. A rating of 1 denoted an absence of paratonic rigidity, whereas a rating of 7 indicated minimal passive force is required for elicitation of the sequence.

With respect to release signs, habituation, duration of response, and intensity were used as criteria for increased activity. A rating of 1 denoted absence of the sign, a rating of 7 indicated an absence of habituation with a persistent response to the repeatedly applied stimulus (more detailed descriptions of the rating methods used for each neurologic variable are available from E.H.F.).

For deep tendon reflexes, plantar response, and muscle tone (paratonic rigidity), an abnormal response in both upper and/or both lower extremities was registered as abnormal. Responses were usually symmetrical, but occasionally, slight asymmetrical responses occurred. In these instances, the higher scores were entered.

In addition to these 14 individual neurological measures, five summary measures, consisting of combinations of all or several measures, were studied. The four deep tendon reflexes were examined as a summary measure. Five individual release signs, namely, sucking (tactile and visual), grasping (hand and foot), and rooting, were combined in one variable called *prehensile release signs.* Three other release signs, namely, the snout reflex, the glabellar blink reflex, and the palmomental reflex, were also combined in one variable, called *nociceptive release signs.* Another summary measure included all of the release signs studied. The final summary measure combined data from the 14 individual measures.

Analysis Procedure

With regard to the activity rating of neurological observations, we examined the findings employing three different cut-offs, reflecting three levels of conservativeness for defining an observation as hyperactive. The least conservative cutoff required an activity rating of 3 or greater, the moderate cutoff a rating of 5 or greater, and the most conservative cutoff required a rating of 7, signifying the highest activity on the neurologic rating measure. This approach was taken so that the possible emergence of neurologic changes in the course of the dementia process could be more adequately assessed (ie, before, as well as after, they appear as unequivocal and prominent signs) and to describe the evolution of neurologic changes in AD using differing criterion variables.

RESULTS

Results were analyzed from two different perspectives: prevalence of hyperactive responses using the three different criteria defining increased activity noted above and the mean activity rating of responses with increasing severity of dementia as measured by GDS stage.

Prevalence of Hyperactive Responses

Figures 1 through 6 plot the percentages of subjects showing hyperactive responses across GDS stages for some of the key neurological variables, using the three different criteria for rating a test response as hyperactive. With the exception of the nociceptive release signs, there was a general trend for an increased prevalence of hyperactive responses with increasing severity of dementia. χ^2 Analyses were used to determine which of the cognitively impaired groups (GDS stages 3 through 7) evidenced a significantly higher prevalence of hyperactivity than did the normal elderly control subjects (GDS stages 1 and 2) for the key neurological variables. These χ^2 analyses were carried out separately for each of the three criteria for rating a response as hyperactive and are summarized in Table 2.

Table 2.—χ^2 Analyses of Prevalence of Neurological Abnormality for Cognitively Impaired Subjects in Comparison With Normal Elderly Control Subjects Using Differentially Strict Ratings for Neurological Abnormality*

Neurological Variable Rating Required for Abnormality	*P* Value in GDS Stages				
	3	4	5	6	7
Any hyperactive neurological response					
≥3	<.05	<.001	<.001	<.001	<.05
≥5	<.05	<.05	<.01	<.001	<.001
7	NS	NS	<.05	<.05	<.001
Any hyperactive deep tendon reflexes					
≥3	<.05	<.01	<.001	<.001	<.01
≥5	NS	NS	NS	<.01	<.01
7	NS	NS	NS	NS	NS
Abnormal plantar response					
≥3	NS	NS	NS	<.01	<.001
≥5	NS	NS	NS	NS	NS
7	NS	NS	NS	NS	NS
Paratonia response					
≥3	NS	NS	<.001	<.001	<.001
≥5	NS	NS	NS	<.001	<.001
7	NS	NS	NS	NS	NS
Prehensile release signs					
≥3	NS	NS	NS	<.001	<.001
≥5	NS	NS	NS	NS	<.001
7	NS	NS	NS	NS	<.001
Nociceptive release signs					
≥3	<.01	<.01	<.01	<.05	NS
≥5	<.05	<.05	<.01	<.05	NS
7	NS	NS	<.01	<.05	<.05

*GDS indicates Global Deterioration scale; NS, not significant ($P < .05$). GDS stages 3 through 7 refer to cognitively impaired subjects in comparison with control subjects (GDS stages 1 and 2). See "Measures" section for explanation of GDS stages.

When all 14 separate scores obtained on deep tendon reflexes, plantar responses, muscle tone, and release signs were combined and examined as one single summary variable (Fig 1), each of the subject groups from GDS stage 4 through stage 7 manifested a significantly higher prevalence than did the control subjects, when hyperactivity was defined either by a rating of 3 or greater or a rating of 5 or greater. When the most conservative criterion was employed (rating of 7), subjects with AD at GDS stages 5, 6, and 7 showed significantly higher prevalence rates than did the control subjects. Interestingly, using both less conservative criteria, significant differences in prevalence were also noted between the patients with only mild but objectively demonstrable cognitive impairment (GDS stage 3) and the control subjects.

Prevalence of hyperactive deep tendon reflexes increased with severity of dementia but only for an activity rating of 3 or greater and 5 or greater (Fig 2). Prevalence of an abnormal plantar response (ie, nonflexor response) was significantly associated with an increase in cognitive decline only for a rating of 3 or greater in the patients with late stages of AD (Fig 3). Prevalence of paratonic rigidity increased significantly with a decline in cognition for an intensity rating of 3 or greater in patients with GDS stages 5 and above, and for an intensity rating of 5 or greater in patients with GDS stages 6 and 7. Five release signs, eg, sucking (tactile and visual), grasping (hand and foot), and rooting, collectively labeled "prehensile release signs," showed the same prevalence pattern (Fig 5). They were absent in control subjects (GDS stages 1 and 2) and in mildly cognitively impaired subjects (GDS stage 3), as well as in subjects with GDS stages 4 and 5. Prevalence for this measure showed a steep increase in the GDS stage 6 and, especially, GDS stage 7 (Fig 5) as compared with control subjects.

Three release signs, ie, the snout reflex, glabellar blink reflex, and the palmomental reflex, collectively labeled "nociceptive release signs," showed an increased prevalence for mildly cognitively impaired subjects (GDS stage 3) and in patients with probable AD at GDS stages 4, 5, and 6, but less generally at GDS stage 7, as compared with control subjects (Fig 6). These release signs are not plotted individually, but they showed the following patterns: The snout reflex showed a noticeable increase from GDS stages 3 through 6, but declined again in GDS stage 7. The glabellar blink reflex and the palmomental reflex were occasionally observed in normal control subjects (GDS stages 1 and 2) and were more prominent in GDS stages 3 through 6 at an activity rating of 3 or greater and 5 or greater. Only one patient in GDS stage 7 had a glabellar blink reflex at an activity rating of 7, the most conservative rating.

Mean Severity of Hyperactive Responses

The data were also analyzed from the viewpoint of mean response activity across the GDS stages (Table 3). When the scores of all 14 neurologic measures (ie, deep tendon reflexes, plantar responses, muscle tone, and release signs) were combined in one summary variable, each of the AD groups (GDS stages 4 through 7), as well as the mildly cognitively impaired group (GDS stage 3), showed a significantly higher mean rating on this summary variable than did control subjects (GDS stages 1 and 2). With respect to deep tendon reflexes, each of the probable AD groups (GDS stages 4 through 7) showed a higher mean value than did control subjects. Patients with AD in GDS stages 5 through 7 had significantly higher mean scores on paratonic rigidity than did control subjects. Patients in each of these GDS stages also had higher mean scores on paratonic rigidity than did patients in the preceding GDS stage. With respect to the prehensile release signs, subjects in GDS stage 6 had significantly higher mean ratings for the hand grasp reflex and the foot grasp reflex compared with control subjects and compared with subjects in GDS stage 5. Subjects in GDS stage 7 had significantly higher mean ratings for the hand grasp and foot grasp reflexes as well as for the visual and tactile sucking reflexes and for the rooting reflex than did subjects in GDS stage 6.

A one-way analysis of variance and Newman-Keuls follow-up procedure for age showed that the control group (GDS stages 1 and 2) was significantly

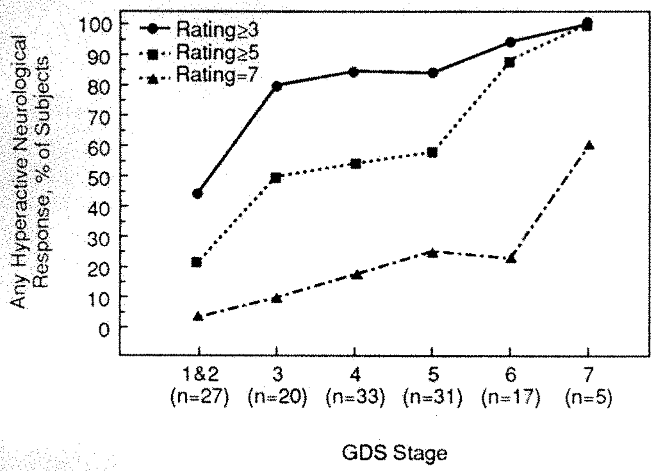


Fig 1.—Percentage of subjects showing any hyperactive neurological response studied (ie, any hyperactive deep tendon reflex, plantar response, muscle tone, or release sign) as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of hyperactivity.

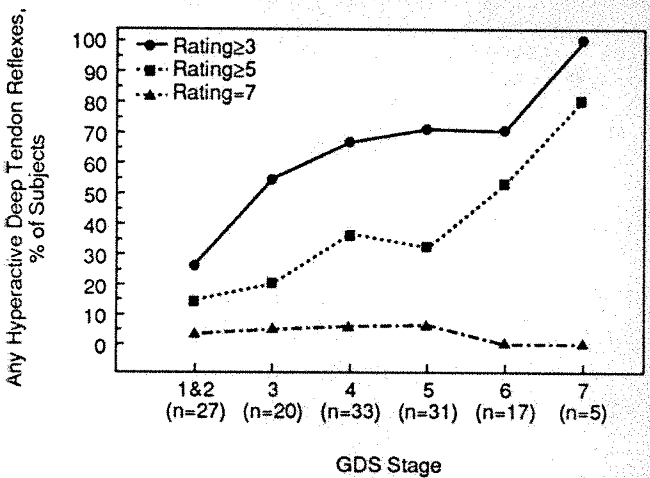


Fig 2.—Percentage of subjects showing any hyperactive deep tendon reflexes (ie, any biceps, triceps, quadriceps, or gastrocnemius-soleus reflex hyperactivity) as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of hyperactivity.

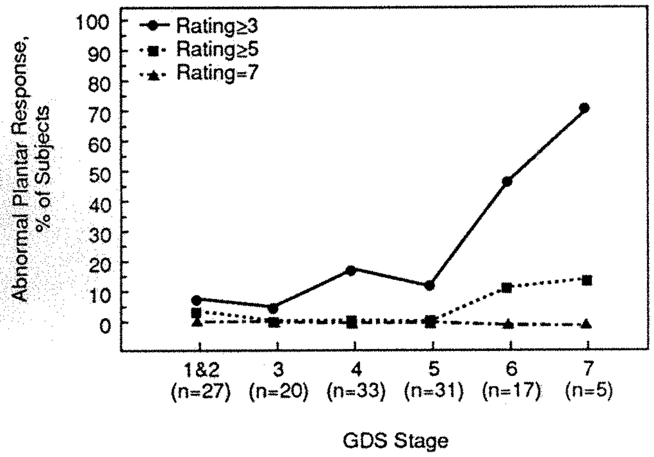


Fig 3.—Percentage of subjects showing an abnormal plantar response as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of abnormality.

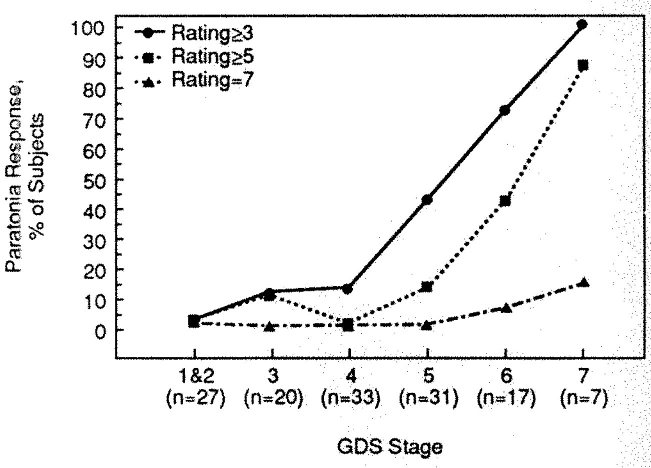


Fig 4.—Percentage of subjects showing paratonia as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of activity.

Fig 5.—Percentage of subjects showing prehensile release signs as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of activity.

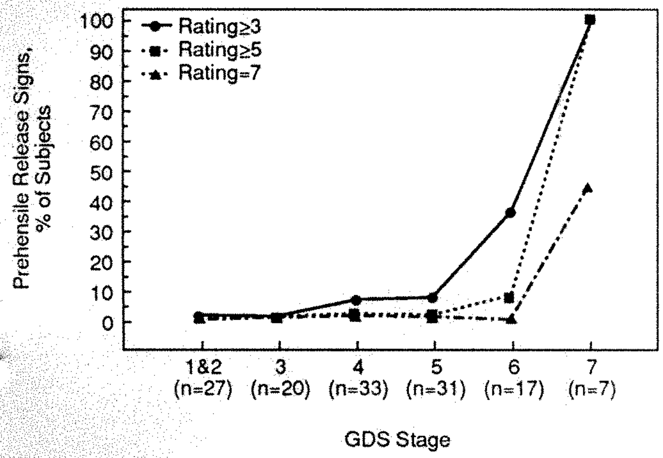
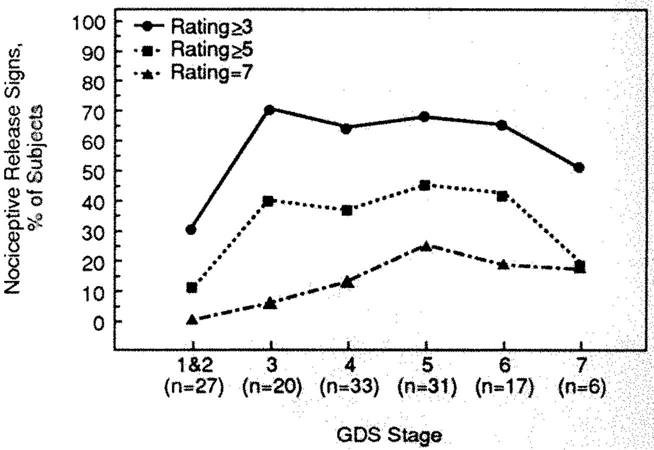


Fig 6.—Percentage of subjects showing nociceptive release signs as a function of the Global Deterioration Scale (GDS) stage, using three different ratings of activity.



younger than the group with the most severe AD (GDS stage 7). Thus, we repeated the above analyses with a subset of the control subjects that were matched in age to the subjects with GDS stage 7. This analysis showed significantly higher mean activity ratings for 12 of the 14 individual neurological variables that showed such differences in Table 3 (biceps and quadriceps reflexes were the only exceptions). Therefore, age differences apparently do not account for the remaining between-group differences observed.

COMMENT

Alzheimer's disease is a slowly escalating neurodegenerative process, insidious in onset, and with extensive neuropathologic changes in the cerebral cortex and subcortical areas.

The classic neurologic examination, as it is commonly used by clinicians, is eminently suited to locate pathogenic factors, but it may not always be a sensitive enough technique for revealing the subtle changes occurring in AD, especially in the early stages. This problem might, to some extent, be addressed by rating the observed clinical signs on a scale and by looking for patterns in groups of individual signs as the illness evolves.

Subjects with the mildest degree of objectively demonstrable impairment (GDS stage 3) in our study did not show statistically significant changes in individual neurologic measures studied. However, they had significantly higher scores on a summary variable that combined the scores of all deep tendon reflexes, plantar responses, muscle tone, and release signs studied, suggesting subtle changes in neurologic function. They also obtained higher scores on deep tendon reflex activity prevalence as a summary measure and on the prevalence of a combination of nociceptive release signs (ie, snout reflex, glabellar blink reflex, and palmomental reflex), as compared with normally functioning healthy elderly control subjects. The prognosis with regard to clinical deterioration of subjects with mild memory impairment (GDS stage 3) is not yet entirely clear. This stage may herald dementia, but not necessarily only of the Alzheimer type.

The trend to increased prevalence of hyperactivity on the combined and individual deep tendon reflex variables studied continued throughout the GDS stages of progressive AD. Plantar responses that were commonly flexor in the early stages of probable AD became less distinctly flexor in the late GDS stages.

Table 3.—Activity Rating of All Neurological Variables and All Combinations of Variables as a Function of Severity of Cognitive and Functional Impairment by GDS*

Neurological Variable	GDS Stage						P†
	1 and 2 (n = 27)	3 (n = 20)	4 (n = 33)	5 (n = 31)	6 (n = 17)	7 (n = 5-7)	
Four deep tendon reflexes, plantar response, muscle tone, and all release sign variables combined (ie, 14 individual variables combined)							
$\bar{X}$	1.25	1.60‡§	1.68‡	1.79‡	2.21‡§	3.84‡§	
SD	0.38	0.51	0.51	0.57	0.71	0.18	<.0001
Four deep tendon reflexes combined							
$\bar{X}$	1.51	2.20	2.38‡	2.52‡	2.91‡	4.30‡§	
SD	1.05	1.25	1.31	1.50	1.58	0.65	<.001
Biceps							
$\bar{X}$	1.48	2.15	2.27	2.58‡	3.18‡	4.00‡	
SD	1.22	1.27	1.59	1.73	1.81	1.55	<.01
Triceps							
$\bar{X}$	1.22	2.00	2.15‡	2.42‡	3.12‡	4.33‡	
SD	0.85	1.26	1.42	1.75	1.80	1.03	<.0001
Quadriceps							
$\bar{X}$	1.81	2.40	2.58	2.68	3.18	4.14‡	
SD	1.47	1.57	1.68	1.78	1.94	1.46	<.05
Gastrocnemius-soleus							
$\bar{X}$	1.52	2.25	2.51	2.42	2.18	3.3	
SD	1.42	1.62	1.91	1.80	1.59	1.86	NS
Plantar response							
$\bar{X}$	1.22	1.10	1.39	1.29	2.29‡§	2.71‡	
SD	0.85	0.45	0.86	0.69	1.53	1.38	<.0001
Muscle tone (paratonia)							
$\bar{X}$	1.00	1.40	1.24	2.10‡§	3.47‡§	5.42‡§	
SD	0.00	1.23	.66	1.45	1.96	0.48	<.0001
All release sign variables combined							
$\bar{X}$	1.15	1.38	1.42‡	1.44‡	1.68‡	3.56‡§	
SD	0.27	0.32	0.42	0.39	0.69	0.48	<.0001
All five prehensile release sign variables combined (sucking, grasping, and rooting)							
$\bar{X}$	1.00	1.00	1.04	1.03	1.35‡§	4.43‡§	
SD	0.00	0.00	0.12	0.10	0.67	1.27	<.0001
Sucking tactile							
$\bar{X}$	1.00	1.00	1.09	1.13	1.41	6.00‡§	
SD	0.00	0.00	0.38	0.50	1.18	1.00	<.0001
Sucking visual							
$\bar{X}$	1.00	1.00	1.03	1.00	1.18	5.43‡§	
SD	0.00	0.00	0.17	0.00	0.73	1.40	<.0001
Hand grasp							
$\bar{X}$	1.00	1.00	1.00	1.00	1.53‡§	4.43‡§	
SD	0.00	0.00	0.00	0.00	0.87	1.62	<.0001
Foot grasp							
$\bar{X}$	1.00	1.00	1.06	1.00	1.65‡§	3.71‡§	
SD	0.00	0.00	0.35	0.00	1.27	1.50	<.0001
Rooting							
$\bar{X}$	1.00	1.00	1.00	1.00	1.00	2.58‡§	
SD	0.00	0.00	0.00	0.00	0.00	2.15	<.0001
All nociceptive release sign variables combined (snout, glabellar blink, and palmomental reflexes)							
$\bar{X}$	1.41	2.02	2.05	2.13	2.24	1.89	
SD	0.72	0.85	1.03	0.97	1.23	1.31	NS
Snout							
$\bar{X}$	1.11	1.10	1.30	1.23	1.88‡§	1.86	
SD	0.42	0.45	0.73	0.72	1.50	1.07	<.05
Glabellar blink							
$\bar{X}$	1.74	2.75	3.15	3.29	3.18	2.00	
SD	1.38	2.05	2.25	2.57	2.55	2.45	NS
Palmomental							
$\bar{X}$	1.37	2.20	1.70	1.87	1.65	1.57	
SD	0.97	1.61	1.31	1.45	1.36	0.98	NS

*Values are mean (± SD). GDS indicates Global Deterioration Scale; NS, not significant ($P > .05$). For explanation of GDS stages see "Measures" section.

†*P* values show significance of change in neurologic variable with GDS (F probability).

‡Significantly different from control subjects (GDS stages 1 and 2) at $P < .05$ (one-way analysis of variance using Newman-Keuls follow-up procedure).

§Significantly different from preceding GDS category at $P < .05$ (one-way analysis of variance using Newman-Keuls follow-up procedure).

A prominent pyramidal syndrome with very active deep tendon reflexes, clonus, and Babinski responses, however, was not seen in any of the GDS stages. Patients with GDS stage 7 frequently had prominent foot-grasp reflexes that presumably could obscure a Babinski response. Sometimes an extensor plantar response could be elicited in these patients by other techniques, such as the Oppenheim reflex or the Gordon reflex.

Release signs were common in all patients with probable AD (GDS stages 4 through 7), a finding also reported by Huff et al.[17] Commonly regarded as evidence of diffuse brain damage, their teleology is presently not clear.[29] The results of this study indicate that from the perspective of AD these signs seem to fall into two different categories. The prehensile release signs (sucking, grasping, and rooting) were associated with the severity of dementia only in the late stages of AD (GDS stages 6 and 7). These signs were not present in patients with early dementia. The grasp reflexes became more prominent in GDS stage 6. This was followed by prominent sucking reflexes and rooting reflexes in patients with GDS stage 7.

Paratonic rigidity, also referred to as paratonia or gegenhalten, is sometimes regarded as a release sign, and it is probably a constituent of the postural reflexes. Paratonia followed a prevalence pattern similar to the prehensile release signs with the exception that it was already prominent in GDS stage 5. All of the patients with GDS stage 7, who displayed all of the prehensile release signs and paratonia prominently, had also lost the ability to ambulate.

De Ajuriaguerra et al[30] have described a prehensile or grasping behavior in patients in the late stage of progressive dementia, following psychomotor disintegration. The authors observed a remarkable similarity between this stereotyped behavior and the oral type behavior of the neonate. They believed that the reemergence of this lower level of neuronal integration is related to the loss of cortical inhibitory function, in accordance with the postulate of Hughlings Jackson that the dissolution process roughly represents subsequent steps down the ontogenetic scale. Paulson and Gottlieb[12] observed simultaneous grasping, sucking, rooting, and muscle hypertonicity in patients with late-stage chronic diffuse brain disease of varying causes. Yakovlev[31] has described the evolution of a syndrome of paraplegia in flexion of cerebral origin, eg, a highly patterned sequence of change in posture observed in the course of mental deterioration in individuals suffering from a severe degenerative cerebral disease. Initially, there was paratonic rigidity on a background of impaired intellectual function, with exaggerated tendon reflexes and Babinski's signs, followed by the gradual evolution of stereotyped behavior with rigidity of posture, spontaneous grasping, and sucking. The end stage was that of profound dementia with pelvicrural flexion contracture, without sensory loss, and, usually, without pyramidal tract signs and with foot-grasp reflexes. Individual hyperactive muscle stretch reflexes were commonly replaced by a mass reflex, as occurs in the fetus. In patients with probable AD, the prehensile signs, with inclusion of paratonia, might presumably be parts of a gradually evolving prehensile syndrome, as described by de Ajuriaguerra et al, and, eventually, of paraplegia in flexion, as Yakovlev has described.

A second group of release signs, namely, snout reflex, glabellar blink reflex, and palmomental reflex, was collectively labeled nociceptive because they each constitute the contraction of one facial muscle in response to a perceived threatening or noxious stimulus. They are probably also closely related to nociceptive skin reflexes.[32] In the present study, these nociceptive signs as a group were less distinctly associated with dementia progression. These signs occurred much earlier in the course of cognitive decline than did the prehensile signs. The prevalence of these signs was generally lower in late-stage dementia (GDS stage 7) as compared with the early and middle stages (GDS stages 4 through 6), and even with the stage of mild memory impairment (GDS stage 3). Observation of these signs in late-stage AD could be obscured by increased presence of sucking, blepharospasm, and facial dyskinesia, which are more common in late-stage AD. Interestingly, these signs are also frequently seen in patients with Parkinson's disease,[33-36] in whom they reverse after levodopa therapy,[36,37] as well as in patients with tardive dyskinesia,[38] dystonic disorders,[39] and human immunodeficiency virus encephalopathy.[40] Habituation of the blink reflex is associated with mature dopaminergic brain circuits.[41] Prominent presence of these signs in AD may be indicative of a subgroup with parkinsonian features and may have implications with regard to the desirability of the use of psychotropic agents, with prominent extrapyramidal side effects, widely prescribed to control the agitation and other behavioral disturbances commonly occurring in AD.

Release signs and pyramidal signs have been reported to predominate in vascular dementia with lacunae, especially in the frontal lobes.[42] Patients with evidence of such lesions on computed tomographic scan or magnetic resonance imaging were excluded from our study. Some of the patients in our study had evidence of periventricular white matter hypodense areas on computed tomographic scan or magnetic resonance imaging, as described by Brun and Englund.[43] Increased impairment of gait has been reported to appear in patients with AD showing these white matter changes, but not in cognitively intact elderly subjects with similar lesions.[44] Whether this particular change had any influence on the occurrence of release signs and pyramidal signs in the subjects of our study requires further investigation.

The finding of subtle neurologic change in mildly cognitively impaired, but not demented, subjects is interesting. Whether it has any consequences for predicting further cognitive deterioration needs to be elucidated.

Some reservation with regard to the present findings is warranted. This is a cross-sectional study. Only a longitudinal study, which is currently in progress, will be able to confirm if the above observed sequence of neurologic changes is characteristic of AD.

Also, the number of subjects in this study was relatively small. We hope to publish a future study with more subjects. The specificity of the above-reported observations with respect to probable AD compared with other forms of dementia also needs further investigation.

We believe, however, that the observations made in this study justify further investigation to determine the usefulness of quantitative measurements of cognition-independent neurologic signs as independent markers of early cognitive impairment and clinical severity of dementia in AD and, perhaps, as indicators for the effectiveness of putative therapeutic agents in the treatment of AD.

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The methodology described herein is the subject of a proposed United States patent application.

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References

1. McDuff T, Sumi SM. Subcortical degeneration in Alzheimer's disease. *Neurology.* 1985; 35:123-126.

2. Katzman R. Alzheimer's disease. *N Engl J Med.* 1986;314:964-973.

3. German DC, White CL, Sparkman DR. Alzheimer's disease: neuro-fibrillary tangles in nuclei that project to the cerebral cortex. *Neuroscience.* 1987;21:305-312.

4. Alzheimer A. Über eine eigenartige Erkrankung der Hirnrinde. *Allg Z Psychiatrie Psychisch-Gericht Med.* 1907;64:146-148.

5. Sjögren T, Sjögren H, Lindgren AGH. Morbus Alzheimer and morbus Pick: a genetic, clinical and patho-anatomical study. *Acta Psychiatr Scand.* 1952;27(suppl 82):69-115.

6. Reisberg B, Ferris SH, Franssen E. An ordinal functional assessment tool for Alzheimer's-type dementia. *Hosp Community Psychiatry.* 1985;36:593-595.

7. Jenkyn LR, Reeves MD. Neurologic signs in uncomplicated aging (senescence). *Semin Neurol.* 1981;1:21-30.

8. Huff FJ, Growdon JM. Neurological abnormalities associated with severity of dementia in Alzheimer's disease. *Can J Neurol Sci.* 1986; 13:403-405.

9. Jacobs L, Gossman MD. Three primitive reflexes in normal adults. *Neurology.* 1980;30:184-188.

10. Basavaraju NG, Silverstone F, Libow L, Paraskeros K. Primitive reflexes and perceptual sensory tests in the elderly: their usefulness in dementia. *J Chronic Dis.* 1981;34:367-377.

11. Jenkyn LR, Reeves AG. Evaluating cortical disinhibition signs. *Neurology.* 1983;33:957.

12. Paulson G, Gottlieb G. Developmental reflexes: the reappearance of foetal and neonatal reflexes in aged patients. *Brain.* 1968;91:37-52.

13. Villenueve A, Turcotte J, Bouchard M, et al. Release phenomena and iterative activities in psychiatric geriatric patients. *Can Med Assoc J.* 1974;110:147-153.

14. Tweedy J, Reding M, Garcia C, et al. Significance of cortical disinhibition signs. *Neurology.* 1982;32:169-173.

15. Wolfson LJ. The neurologic consultation at age 80. In: Katzman R, Terry R, eds. *The Neurology of Aging.* Philadelphia, Pa: FA Davis Co; 1983:221-244.

16. Klawans HL, Tufo HM, Ostfeld AM, et al. Neurologic examination in an elderly population. *Dis Nerv Syst.* 1971;32:274-279.

17. Huff HL, Boller F, Luchelli F, Querriera R, Beyer J, Belle S. The neurologic examination in patients with probable Alzheimer's disease. *Arch Neurol.* 1987;44:929-932.

18. Mohs R, Kim Y, Johns C, Dunn D, Davis K. Assessing changes in Alzheimer's disease: memory and language. In: Poon LW, ed. *Handbook for Clinical Memory Assessment.* Washington, DC: American Psychological Association; 1986:149-155.

19. Wilson R, Kaszniak A. Longitudinal changes: progressive idiopathic dementia. In: Poon LW, ed. *Handbook for Clinical Memory Assessment.* Washington, DC: American Psychological Association; 1986:285-293.

20. Reisberg B, Ferris SH, de Leon MJ, et al. Stage-specific behavioral, cognitive, and in vivo changes in age-associated memory impairment (AAMI) and primary degenerative dementia of the Alzheimer type. *Drug Dev Res.* 1988;15:101-114.

21. Kaye J. Neurochemical aspects of motor impairment. In: Friedland RP, moderator. Alzheimer disease: clinical and biological heterogeneity. *Ann Intern Med* 1988;109:298-311.

22. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* 1984;34:939-944.

23. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemia score in differentiation of dementias. *Ann Neurol.* 1980;7:486-488.

24. Reisberg B, Ferris SH, de Leon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry.* 1982;139:1136-1139.

25. Folstein MF, Folstein SE, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

26. Mayo Clinic and Mayo Foundation. *Clinical Examinations in Neurology.* 5th ed. Philadelphia, Pa: WB Saunders Co; 1981:168-179.

27. Paulson GW. The neurological examination in dementia. In: Wells CE, ed. *Dementia.* 2nd ed. Philadelphia, Pa: FA Davis Co; 1977:169-188.

28. Coghill GE. Flexion spasms and mass reflexes in relation to the ontogentic development of behavior. *J Comp Neurol.* 1943;79:463-486.

29. Landau WM. Reflex dementia: disinhibited primitive thinking. *Neurology.* 1989;39:133-137.

30. de Ajuriaguerra J, Rego A, Tissot R. Le reflexe oral et quelques activités orales dans les syndromes dementiels du grand age: leur signification dans la desintegration psycho-motrice. *Encephale.* 1963;52:179-219.

31. Yakovlev P. Paraplegia in flexion of cerebral origin. *J Neuropathol Exp Neurol.* 1954; 13:267-296.

32. Reis DJ. The palmomental reflex, a fragment of a general nociceptive skin reflex: a physiological study in normal man. *Arch Neurol.* 1961;4:486-498.

33. Pearce J, Aziz M, Gallagher JC. Primitive reflex activity in primary and symptomatic parkinsonism. *J Neurol Neurosurg Psychiatry.* 1968;31:501-508.

34. Dalby MA. The diagnostic value of the palmomental reflex. *Acta Neurol Scand.* 1970;46:601-608.

35. Klawans HL, Paulson GW. Primitive reflexes in parkinsonism. *Confin Neurol.* 1971;33:25-32.

36. Maertens de Noordhout A, Delwaide PT. The palmomental reflex in Parkinson's disease: comparisons with normal subjects and clinical relevance. *Arch Neurol.* 1988;45:425-427.

37. Klawans HL, Goodwin JA. Reversal of the glabellar reflex in parkinsonism by L-dopa. *J Neurol Neurosurg Psychiatry.* 1969;32:423-427.

38. Youssef H, Waddington JL. Primitive (developmental) reflexes and diffuse cerebral dysfunction in schizophrenia and bipolar affective disorder: overrepresentation in patients with tardive dyskinesia. *Biol Psychiatry.* 1988;23:791-796.

39. Cohen LG, Ludlow CL, Warden M, et al. Blink reflex excitability-recovery curves in patients with spasmodic dystonia. *Neurology.* 1989;39:572-577.

40. Teschke RS. A tetrad of neurologic signs sensitive to early human immunodeficiency virus brain disease. *Arch Neurol.* 1987;44:693.

41. Zametkin AJ, Stevens JR, Pittman R. Ontogeny of spontaneous blinking and of habituation of the blink reflex. *Ann Neurol.* 1979;5:453-457.

42. Ishi N, Nishihara Y, Imamura T. Why do frontal lobe symptoms predominate in vascular dementia with lacunas? *Neurology.* 1986;36:340-345.

43. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol.* 1986;19:253-262.

44. George AE, de Leon MJ, Gentes CI, et al. Leukoencephalopathy in normal and pathologic aging, I: CT of brain lucencies. *AJNR.* 1986;7:561-566.

Age at Onset of Alzheimer's Disease

Relation to Language Dysfunction

Kathryn A. Bayles, PhD

• A later age at onset of Alzheimer's disease (AD) was found to be related to diminished language performance in 86 patients with probable AD. A hierarchical linear model was constructed to assess effects of age at onset and disease duration on the performance of patients with AD on four language tasks (naming, reading, auditory comprehension, and writing to dictation) after controlling for disease severity. Results of univariate analysis, in which the dependent variable was the averaged language task performances, revealed a significant effect for age at onset of AD, but not for disease duration. To assess the possibility that the relationship between the age at onset of AD and language performance reflects effects of normal aging, the language tasks were given to 33 normal subjects of similar ages who scored perfectly on dementia severity measures. A convincing relationship was not found between test score and age.

(*Arch Neurol.* 1991;48:155-159)

Reports of heterogeneity in the neurobehavioral deficits in patients with Alzheimer's disease (AD) suggest the existence of clinical subgroups. One possible subgroup comprises individuals with an early onset of AD who have been reported to have language deficits more than would patients with late onset.[1-4]

Seltzer and Sherwin[1] classified 65 patients with AD as normal or abnormal in language function by performance on tasks modified from the Boston Diagnostic Aphasia Examination.[5] Proportionately more individuals with early age at onset of AD were present in the linguistically abnormal group than were in the linguistically normal group. Faber-Langendoen and colleagues[2] observed aphasic subjects with AD to be younger at onset of dementia than their nonaphasic counterparts. Filley et al,[3] who also administered portions of the Boston Diagnostic Aphasia Examination to patients with AD with early and late onset, reported greater language disorder in patients with early onset, but not as measured by the Boston Diagnostic Aphasia Examination subtests. Age-at-onset effects were apparent only on the Reitan-Indiana Aphasia Screening Test.[6] Using performance on the eight language-related items in the Mini-Mental State Examination (MMSE)[7] to detect aphasia, Chui and colleagues[4] reported 60% of their 146 patients with AD to be aphasic and the proportion of early-onset cases to be higher in the aphasic group compared with that in the nonaphasic group.

Reports of greater language impairment in patients with an early onset of AD have been challenged. Selnes et al[8] and Grady et al[9] failed to find a significant relationship between age at onset of AD and language deficit, and Cummings and colleagues[10] report language impairment in all their patients with AD that is proportional to severity of dementia.

Regardless of whether the aforementioned investigators found a relationship between age at onset of AD and language performance, none of them employed methodology whereby each subject's language score(s) was controlled for the effect of dementia severity, a necessary control because of the well-documented relationship between dementia severity and language score.[6,8,10,11] Such control subjects were employed in a large study of the effects of AD on language function. The purpose of this report is to present evidence that when effects of dementia are controlled, age at onset is related to degree of language deficit in such a way that the older the age at onset, the greater the degree of language impairment.

SUBJECTS AND METHODS

Subjects

Eighty-six individuals diagnosed with probable AD according to National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disease Association task force criteria[12] and 42 normal elderly control subjects participated in the study. Patients with probable AD had a history of progressive mental deterioration, including deficits in memory and at least one additional cognitive function. Subjects underwent thorough physical and neurological examinations performed by an experienced neurologist, independent neurobehavioral assessment, and standard laboratory testing. Excluded from the study were individuals who, by history, examination, or laboratory study, demonstrated a systemic or other

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Table 1.—Characteristics of Patients With Alzheimer's Disease (AD) and Normal Elderly Subjects*

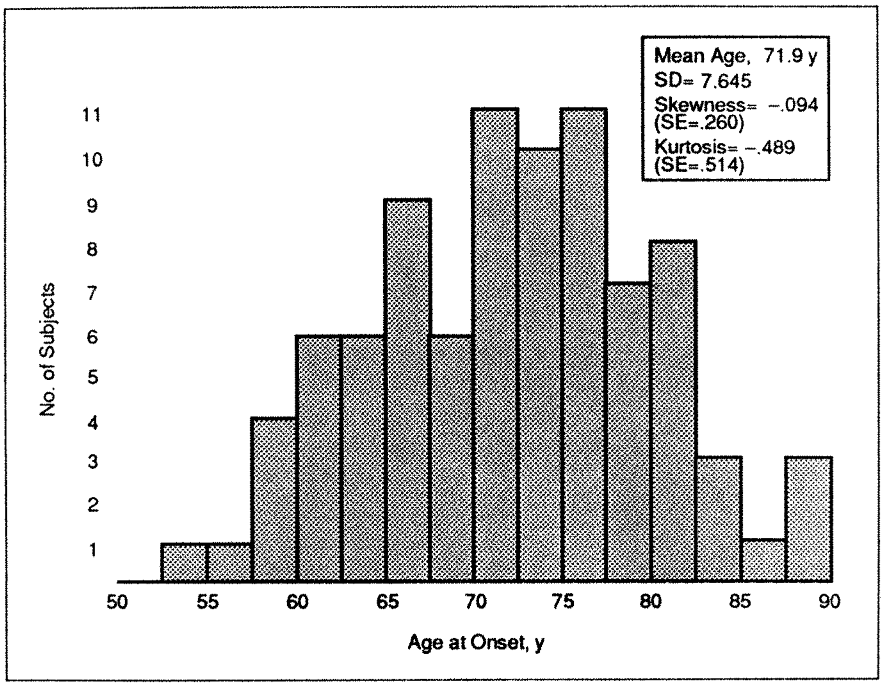
	Patients With AD/Normal Subjects			
Variable	**Mean**	**SD**	**Minimum**	**Maximum**
Age, y	76.59/73.40	7.56/7.59	58.18/61.57	94.51/93.49
Education, y	13.06/14.55	3.19/3.16	4.00/8.00	22.00/21.00
Estimated IQ	110.89/113.11	7.63/7.53	93.39/99.72	132.40/132.00

*The AD group (n = 86) consisted of 32 males and 54 females; the normal group (n = 42) consisted of 10 males and 32 females.

Table 2.—Questionnaire About the Presence of 25 Symptoms of Alzheimer's Disease

Which of the following symptoms have you noticed and when?

1. Complaints of memory problems
2. Problems in concentrating
3. Decreased knowledge of current or recent events
4. Forgetting information about his/her own personal history
5. Decreased ability to travel
6. Decreased ability to handle finances
7. Denies problems
8. Inability to perform complex tasks
9. Withdrawal from challenging situations
10. Forgetting where familiar objects were placed
11. Forgetting names formerly known well
12. Being lost or confused when traveling to familiar places
13. Coworkers aware of problem performing
14. Word- and name-finding problems apparent
15. Reading, but not retaining, information
16. Losing or misplacing objects of value
17. Sleep disturbance
18. Largely unaware of all recent experiences in his/her life
19. Difficulty remembering names of close family members
20. Unaware of his/her surroundings or environment
21. Incontinence
22. Change in personality
23. Change in mood (depressed, agitated, etc)
24. Movement problems
25. Fatigue



The distribution and range of perceived age at onset of Alzheimer's disease.

central nervous system disease associated with intellectual deterioration. Also excluded were individuals with a score of 4 or more on the modified Hachinski Ischemic Scale[13,14] and 12 or more on the Hamilton Depression Rating Scale.[15] Dementia severity was determined by score on the Global Deterioration Scale (GDS)[16] and answers to the questions from the MMSE[7] related to place, time, and the ability to copy.

In addition to the aforementioned exclusionary criteria, the patients with probable AD and normal control subjects had to meet the following inclusionary criteria: pass a speech discrimination test with 80% or better accuracy (see Bayles et al[17] for description), be literate and able to read newsprint, speak English as a first language, have no history of drug or alcohol abuse, and have normal intelligence as estimated by a regression equation using demographic information.[18] The demographic characteristics of study participants are shown in Table 1.

Perceived Age at Onset

Perceived age at onset of AD was specified by primary caregivers after reviewing with the examiner the neurobehavioral features of the disease and their patients' social and medical histories. Before the examiner reviewed the behavioral symptoms of the disease, the caregiver informants were asked to specify the first four symptoms that they observed and the approximate date of their appearance. Subsequently, they were questioned about the presence of 25 symptoms of the disease (Table 2), and asked to specify the time of appearance of those observed in the patient.

The date of the first report of memory impairment was used as the time of onset that was subtracted from the patient's age at testing to obtain perceived age at onset of AD, the datum used in study analyses (mention must be made of the fact that it is impossible to verify caregivers' reports of symptoms). The distribution and range of perceived age at onset of AD are presented in the Figure. Because this distribution is evidently continuous and unimodal (and apparently normal), age at onset is not dichotomized into early and late subgroups.

Duration of dementia was calculated by subtracting the date of onset from the date of testing. The mean disease duration for patients with AD was 4.67 years (SD = 2.37 years).

Tasks

The linguistic communication tasks administered in this study included confrontation naming, auditory comprehension, writing to dictation, and reading comprehension. The tasks, which used the same stimuli, were administered in the order listed herein. In the confrontation naming, task subjects were asked to name 13 black-and-white line drawings presented individually. The objective of the auditory comprehension task was to select, from among four, the correct colored photograph of the object named by the examiner. In the dictation task, the examiner read each word aloud and the subject was required to write the words on a sheet of paper. In the reading comprehension task, the subject had to read the printed name of an object and select the photograph of the object *from* among four photographs of objects.

Table 3.—Effect of Disease Duration and Age at Onset of Disease on Average Language Performance After Controlling for Disease Severity*

Source of Variation	Sum of Squares	*df*	Mean Square	F	*P*
Constant	6628.20	1	6628.20	1941.43	.000
GDS†	109.55	1	109.55	32.09	.000
Place‡	103.10	1	103.10	30.20	.000
GDS by place	18.38	1	18.38	5.38	.023
Copy§	30.75	1	30.75	9.01	.004
GDS by copy	11.09	1	11.09	3.25	.075
Duration	.06	1	.06	.02	.897
Onset‖	22.08	1	22.08	6.47	.013
Error	266.30	78	3.41	. . .	. . .

*Each term is tested after controlling for the terms above it.

†GDS (Global Deterioration Scale) is a categorical variable for which subjects with a score of 3 or 4 were classified as mild; subjects with a GDS score of 5 were classified as moderate.

‡Place indicates subject's scoring on the five orientation questions about place on the Mini-Mental State Examination.

§Copy is a categorical variable that indicates whether or not subject successfully copied the figure on the Mini-Mental State Examination.

‖The 95% confidence interval for the onset coefficient was (−.128, −.015). The negative sign of the coefficient indicates that larger values of the onset variable are associated with smaller values of the language variable.

Table 4.—Effect of Age at Disease Onset on Four Language Variables After Controlling for Disease Severity

Variable	Coefficient	SE	*t*	*P*
Confrontation naming	−.112	.043	−2.58	.012
Auditory comprehension	−.115	.034	−3.38	.001
Writing from dictation	.033	.047	.69	.489
Reading comprehension	−.093	.036	−2.57	.012

Table 5.—Average Age by Scores on Four Language Tasks for 33 Normal Subjects With No Severity Deficits

Score	n	Mean Age, y	SD
Confrontation naming*			
7	1	69.5	. . .
8	1	84.4	. . .
10	1	71.2	. . .
11	8	71.4	5.0
12	9	72.6	6.6
13	13	68.8	4.7
Auditory comprehension†			
12	5	73.7	10.6
13	28	70.6	4.6
Writing from dictation‡			
7	2	65.5	5.6
9	1	71.2	. . .
10	3	71.4	3.8
11	8	71.7	4.2
12	11	70.2	7.4
13	8	72.8	5.7
Reading comprehension			
12	1	71.0	. . .
13	32	71.0	5.8

*Jonckheere's test for negative trend over scores of 11 through 13 was not statistically significant ($z = 1.29$, $P = .10$).

†Welch's approximate t test between scores of 12 and 13 was not statistically significant, $t(4.27) = .64$; two-sided $P = .276$.

‡Jonckheere's test for negative trend over scores of 11 through 13 was not statistically significant ($z = -.27$, $P = .61$).

RESULTS

A general linear model was constructed to assess the extent to which disease severity, disease duration, and age at onset of AD predict language performance. Severity variables comprised GDS, MMSE place questions, MMSE time questions, and the MMSE figure copy task. The model was hierarchical, ie, each term in the model was tested after controlling for the terms that preceded it. By considering the severity variables first, it was possible to assess the effects of disease duration and age at onset on language performance after controlling for disease severity.

Initially, the effects of all possible terms on language performance were considered; eventually, nonsignificant terms were removed from the model (eg, subjects' scores on the five orientation questions about time) to make it as parsimonious as possible. This model was employed in a univariate analysis, in which the dependent variable was the average performance on the four Arizona language tasks, and a multivariate analysis, in which the dependent variables were the separate performances on the four tasks.

Univariate Analysis

Results of univariate analysis, presented in Table 3, revealed several interesting facts about the measurement of disease severity in relationship to language performance. First, the simple task of copying a figure yields significant information about language performance even after controlling for GDS score and performance on MMSE place orientation questions. Second, after controlling for GDS score and place orientation questions, time orientation questions yield no significant information. Third, although the GDS score is based on observation of myriad patient characteristics, MMSE place orientation questions alone turn out to be more informative. Together these terms account for a sum of squares of 212.65 and if the effect of GDS is removed first from this total, MMSE place orientation questions additionally account for 103.10 (48.5%). However, if orientation to place is considered first, it alone is able to account for 200.63 (94.3%), nearly all of the variation attributed to both measures.

With respect to the variables of interest in this study, it is evident that any effect of disease duration on language performance is entirely accounted for by the objective measures of disease severity. On the other hand, even after controlling for disease severity, it appears that age at onset of AD is significantly related to language performance. Moreover, inspection of the model coefficients revealed that *later* onset is associated with diminished performance, the reverse of what many authors have reported.[1-4]

Because F tests are often sensitive to nonnormality and heteroscedasticity, it was deemed advisable to verify the above relationship by a more robust procedure. Accordingly, age at onset of AD was removed from the model. The residuals from this restricted model represent each subject's language score after adjusting for dementia severity. These adjusted language scores were then nonparametrically correlated with age at onset, and the same relationship was observed (Kendall's $\tau = -.1639$, $P = .025$).

Multivariate Analysis

More detailed insight into the relationship between age at onset of AD and language performance may be gained from the multivariate analysis. The effect of age at onset of AD on each of the four language variables is reported in Table 4. It becomes apparent that age at onset is negatively associated with performance on the confrontation naming, auditory comprehension, and reading comprehension tasks, but it is unassociated with performance on the dictation task.

Effects of Normal Aging

The above analyses demonstrate a relationship between age at onset of AD and language performance for subjects with AD. However, it is important to emphasize that age at onset is highly correlated with age at testing ($r = .9516$), an association that raises the possibility that the relationship observed between age at onset and language performance is due to the effects of normal aging. Certainly, the variables employed to quantify severity of dementia can be expected to have removed the (presumably gross) effects of normal aging on subjects with AD, but it is, nonetheless, conceivable that a language-specific component to the aging process still remains. It would be satisfying if the issue of the possibility of residual aging effects on the language performance of the subjects with AD could be resolved by introducing age at testing into the hierarchical general linear model previously employed. Unfortunately, the high correlation between age at testing and age at onset in subjects with AD precludes such a solution; this is known as the problem of multicollinearity in linear models. Therefore, an assessment of the residual effects of normal aging must be based on the distribution of language scores of normal subjects.

One method of assessment would be to apply the same general linear modeling procedure to data from normal subjects. If, after controlling for the effects of the severity variables, age at testing was not a significant predictor of language performance, it could be concluded that the effects of normal aging were removed by the severity variables. It would then follow that the age-at-onset effect detected in subjects with AD was something distinct from normal aging. However, only nine of the 42 normal subjects exhibited deficits in any of the severity variables and, thus, there was insufficient variability in the severity variables to adequately test the model. Nevertheless, severity can be controlled by taking a single group of normal subjects who are all at the same level of severity and examining the relationship between age at testing and language performance within that group. Only one such group existed, namely, the group of 33 subjects with no severity deficits. Table 5 contains the data regarding these subjects and demonstrates how age at testing varied with language performance for them. Notice that the data fail to convincingly support the argument that performance on these four simple tasks declines with normal aging. Nonetheless, that possibility cannot be completely discounted.

COMMENT

Early age at onset of AD, as specified by caregivers, was not found to be related to greater language impairment in a large sample of subjects with AD for whom severity of dementia was controlled. Rather, a subtle, but robust, relationship was found between later age at onset of AD and greater language impairment. Analysis of performance on the individual tasks indicated the presence of this relationship for confrontation naming and auditory and reading comprehension, but not for writing to dictation. Disease effects on writing to dictation may be less severe, because the task is mechanical, cognitively less effortful, and, possibly, can be completed without involvement of semantic (conceptual) memory.

The high correlation between age at onset and age at testing raised the possibility that this relationship was due to the effect of normal aging. This possibility was explored by examining the effect of age at testing on language performance of normal subjects. When the average age at testing for each language score was reviewed, no convincing relationship was observed.

Results of the present study may differ from those of investigators[1-4] reporting a relationship between early disease onset and more prominent language deficits, because the language performance scores of individual participants in this study were controlled for dementia severity. In the Seltzer and Sherwin study,[1] severity of dementia was controlled by testing limited to those individuals who retained "a sufficient level of general intellectual function to engage in testing"[1,p145] and by controlling the early- and late-onset groups for disease duration. Disease duration may not accurately measure degree of dementia severity in view of the reports[2,19-21] that some patients with AD have a rapidly progressing disease, whereas others have a slowly progressing disease.

The report by Filley et al[3] that their early-onset group had greater language impairment was based on the results of performance on seven language measures. Yet, on only one of the seven language measures was the early-onset group significantly more impaired. Further, although the authors reported a trend toward greater impairment by early onset in the word discrimination and complex ideational material subtests of the Boston Diagnostic Aphasia Examination, the mean scores of the early- and late-onset groups on these tasks were extremely close (early-onset group mean for word discrimination was 68.62, and late-onset group mean was 68.00; early-onset group mean for complex ideational material was 8.81, and late-onset group mean was 9.18) and the associated probability values were $P = .73$ in both cases. The single test for which a significantly greater impairment was observed in the patients with early onset of AD was the Reitan-Indiana Aphasia Screening Test.[6] However, no information was given about the test and the number of false-positive results typically associated with it. Finally, patients in the early-onset group may have been premorbidly less gifted in language and general intellectual ability than those in the late-onset group. Indeed, they were scored lower in full-scale, verbal, and performance IQ than were patients in the late-onset group. Although only the differences in full-scale and verbal IQ were significantly different, the pattern was the same for all three measures.

Chui and colleagues[4] used eight items from an MMSE and clinical observation of paraphasias, word-finding difficulty, or reduction in speech output to define language deficit. No information was provided as to what constituted significant numbers of paraphasic errors or word-finding difficulty. Sixty percent of the patients with AD were designated as aphasic, but these individuals were also more severely demented. Indeed, the authors reported that "presence and severity of aphasia were significantly associated with greater severity on the GDS ($t = 6.7$, $P < .0001$)."[4,p1546] Thus, the poorer language performance by the aphasic patients may simply reflect more severe dementia.

Faber-Langendoen et al[2] used performance on a brief clinical aphasia battery to dichotomize their group of 150 subjects with AD into aphasic and nonaphasic subgroups. Thereafter, the authors calculated the mean age at onset of AD for each group and reported that the mean age for the aphasic group was significantly lower. However, the difference in mean ages was only 2.8 years.

The results of the present study

were harmonious with those of Selnes et al,[8] although the question can be asked why these investigators did not report a relationship between later age at onset and greater language impairment. Perhaps the reason was that Selnes and colleagues used the MMSE scores, which are heavily dependent on language performance, for controlling dementia severity in their groups with early and late age at onset of AD.

Grady and colleagues,[9] who also failed to find a relationship between early age at onset and greater language impairment, did not control the effects of dementia severity on language performance on a subject-by-subject basis and perhaps, therefore, failed to detect the subtle relationship between later age at onset and greater language impairment reported in the present study. The variability within the early- and late-onset groups in the Grady study may have been enough to mask this subtle effect.

In summary, a relationship between early age at onset of AD and greater language impairment was not confirmed by results of this study. Rather, a subtle, but statistically significant, relationship was observed between a later age at onset of AD and greater language impairment. The procedure of controlling for the effects of dementia severity on language performance scores on a subject-by-subject basis likely accounts for the principal differences between this study and those of other investigators.

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References

1. Seltzer B, Sherwin I. A comparison of clinical features in early- and late-onset primary degenerative dementia: one entity or two? *Arch Neurol.* 1983;40:143-146.
2. Faber-Langendoen K, Morris JC, Knesevich JW, LaBarge E, Miller JP, Berg L. Aphasia in senile dementia of the Alzheimer type. *Ann Neurol.* 1988;23:365-370.
3. Filley CM, Kelly J, Heaton RK. Neuropsychological features of early- and late-onset Alzheimer's disease. *Arch Neurol.* 1986;43:574-576.
4. Chui HC, Teng EL, Henderson VW, Moy AC. Clinical subtypes of dementia of the Alzheimer type. *Neurology.* 1985;35:1544-1550.
5. Goodglass H, Kaplan E. *The Assessment of Aphasia and Related Disorders.* Philadelphia, Pa: Lea & Febiger; 1972.
6. Reitan RM. *Aphasia and Sensory-Perceptual Deficits in Adults.* Tucson, Ariz: Reitan Neuropsychological Laboratories Inc; 1984.
7. Folstein M, Folstein S, McHugh P. The Mini-Mental State Examination. *J Psychiatr Res.* 1975;12:189-198.
8. Selnes OA, Carson K, Rovner B, Gordon B. Language dysfunction in early- and late-onset possible Alzheimer's disease. *Neurology.* 1988;38:1053-1056.
9. Grady CL, Haxby B, Horwitz B, Berg G, Rapoport SI. Neuropsychological and cerebral metabolic function in early vs late onset dementia of the Alzheimer type. *Neuropsychologia.* 1987;25:807-816.
10. Cummings JL, Benson F, Hill MA, Read S. Aphasia in dementia of the Alzheimer type. *Neurology.* 1985;35:394-397.
11. Bayles KA, Kaszniak AW. *Communication and Cognition in Normal Aging and Dementia.* San Diego, Calif: College-Hill, 1987.
12. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease. *Neurology.* 1984;34:939-944.
13. Hachinski VC, Iliff LD, Zilhka E, et al. Cerebral blood flow in dementia. *Arch Neurol.* 1975;32:632-637.
14. Rosen WG, Terry RD, Fuld PA, Katzman R, Peck A. Pathological verification of ischemic scores in differentiation of dementia. *Ann Neurol.* 1980;7:486-488.
15. Hamilton MA. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62.
16. Reisberg B, Ferris SH, DeLeon MJ, Crook T. The global deterioration scale for assessment of primary degenerative dementia. *Am J Psychiatry.* 1982;139:1136-1139.
17. Bayles KA, Boone DR, Tomoeda CK, Slauson TJ. Differentiating Alzheimer's patients from the normal elderly and stroke patients with aphasia. *J Speech Hear Disord.* 1989;54:74-87.
18. Wilson RS, Rosenbaum G, Brown G. The problem of premorbid intelligence in neuropsychological assessment. *J Clin Neuropsychol.* 1979;1:49-53.
19. Huff FJ, Growdon JH, Corkin S, Rosen TJ. Age at onset and rate of progression of Alzheimer's disease. *J Am Geriatr Soc.* 1987;35:27-30.
20. Berg L, Danziger WL, Storandt M, et al. Predictive features in mild senile dementia of the Alzheimer's type. *Neurology.* 1984;34:563-569.
21. Botwinick J, Storandt M, Berg L. A longitudinal, behavioral study of senile dementia of the Alzheimer's type. *Arch Neurol.* 1986;43:1124-1127.

Anatomic, Metabolic, Neuropsychological, and Molecular Genetic Studies of Three Pairs of Identical Twins Discordant for Dementia of the Alzheimer's Type

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• Three pairs of twins, each with proved monozygosity, were shown to be discordant for dementia of the Alzheimer's type and to have remained discordant for periods of 8 to 11 years. Dementia of the Alzheimer's type was demonstrated by history; serial clinical examinations; serial measurements of cerebral glucose utilization using positron emission tomography and of cerebral ventricular volumes and of rates of change of volumes using quantitative computed tomography; and by serial neuropsychological tests. The results of each of these measures showed no evidence of clinical abnormality in any unaffected twin. DNA markers from the proximal long arm of chromosome 21 did not distinguish between the affected and the unaffected member of any pair of identical twins. Family pedigrees were negative for Alzheimer's disease. The results suggest that environmental or other nongenetic factors contribute to Alzheimer's disease in discordant monozygotic twins, or that some cases arise by a postzygotic somatic mutation.

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Alzheimer's disease is a progressive neurodegenerative disorder that is the most common cause of dementia in the United States, but its precise cause is unknown. It affects about 5% of individuals older than 65 years and 10% to 15% of those older than 80 years of age.[1] Established risk factors are age and familial aggregation. An autosomal dominant mode of transmission with a lifetime (90-year) risk of 50% among first-degree relatives of probands has been reported.[2,3] Reports of Alzheimer's disease in twins suggest a 40% to 50% concordance for the disease in monozygotic twins and an 8% to 50% concordance in dizygotic twins.[4-18]

Of these reports, only two[6,13] describe twins discordant for dementia of the Alzheimer's type (DAT) with proved monozygosity and with neuropathological proof of Alzheimer's disease in the affected twin. No report provides detailed proof of discordance in proved monozygotic twins, using studies of brain anatomy and metabolism with computed tomography (CT) and positron emission tomography (PET), respectively, and a complete battery of cognitive tests. Furthermore, no study of monozygotic twins discordant for DAT has been longitudinal in nature. However, as age at onset of DAT may differ by up to 11 years between twins with documented monozygosity who eventually become concordant,[15] a finding of discordance in a single cross-sectional analysis may be of limited value for estimating the true discordance rate, or even for establishing discordance in a given pair of monozygotic twins.[9,19] We, therefore, thought it important to further examine the discordance of Alzheimer's disease in monozygotic twins. To do this, we document, in a longitudinal experimental design, differences in brain metabolism, cognitive function, and neuroanatomy in three pairs of monozygotic twins thought to be discordant for DAT and provide neuropathological confirmation of Alzheimer's disease in one of the affected twins. By evaluating social and medical histories, as well as environmental exposure of each of the twins, and by examining DNA markers from chromosome 21,[20,21] we try to distinguish an environmental or genetic factor that might contribute to Alzheimer's disease. Finally, because of the approximately 40% concordance rate of DAT in monozygotic twins,[14] we thought it possible, using sensitive measures of brain function and anatomy, that one of the unaffected twins from the three twin pairs might show early, preclinical changes of DAT. Our results have been partially reported in abstract form.[22]

SUBJECTS AND METHODS

Subjects

Our subjects were two male twin pairs, 1A* and 1B and 2A* and 2B; and one female twin pair, 3A* and 3B. Asterisk denotes the twin with a diagnosis of DAT, probable

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Alzheimer's disease, using the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Diseases Association criteria.[23] The twins 1A* and 1B were described partially by Luxenberg et al[24] and had been identified from the Twin Registry of the National Academy of Sciences, National Research Council (see the acknowledgments).[25] Each subject signed an informed consent to participate in the study.

Detailed histories were obtained for each subject. Each twin also underwent comprehensive physical and neurologic examinations, and the following tests were performed: electrocardiogram, a chest roentgenogram, CT of the head, an electroencephalogram, and routine laboratory tests, including complete blood cell count, differential white blood cell count, VDRL test, and measurements of blood levels of urea, as well as creatinine, antinuclear antibody, vitamin B_{12}, folate, and thyroid hormone levels. Each twin underwent PET, quantitative CT, and extensive cognitive testing, as described below. Depending on compliance, the procedures were repeated one to three times over periods of up to 3 years.

Age-matched volunteers were used as control subjects. They were screened rigorously for medical or neurological illness, and met stringent health criteria as previously described.[26] Different control groups were used for each of the neuropsychological, PET, and CT studies. For cross-sectional CT studies, there were 25 male control subjects with a mean age (±SD) of 61 ± 6 years, and 19 female control subjects with a mean age (±SD) of 60 ± 6 years. For longitudinal CT studies, male (n = 7) mean age (±SD) was 61 ± 6 years, and female (n = 4) mean age (±SD) was 58 ± 5 years. For the PET control subjects, using the ECAT II scanner (ORTEC, Life Sciences, Oak Ridge, Tenn), male (n = 18) mean age was 60 ± 3 years and female (n = 6) mean age was 62 ± 3 years, and using the Scanditronix (Uppsala, Sweden) scanner, male (n = 8) mean age was 59 ± 4 years and female (n = 22) mean age was 62 ± 6 years. Control subjects for the neuropsychological tests are described below.

Procedures

PET.—Each subject underwent PET using ^{18}F-2-fluoro-2-deoxy-D-glucose to determine regional cerebral metabolic rates for glucose ($rCMR_{glc}$). The procedure was carried out in the early part of the study, using an ECAT II tomograph (ORTEC) with in-plane and axial resolutions of 17 mm. Beginning May 1986, a more sensitive PC 1024 PET tomograph (Scanditronix) was employed, with an in-plane resolution of 6 mm and an axial resolution of 10 mm.

A subject was kept drug free for at least 2 weeks prior to a scan, refrained from alcohol, caffeine, and nicotine use for at least 24 hours, and fasted for 2 hours prior to the scan. The scan was performed with the subject supine in a quiet room, his eyes covered, and his ears plugged with cotton. Details of PET scanning on both machines have been presented elsewhere.[26-30]

The $rCMR_{glc}$ was calculated in milligrams of glucose consumed per 100 g of brain per minute ($mg \cdot 100\ g^{-1} \cdot min^{-1}$). We also calculated normalized metabolic ratios, defined as $rCMR_{glc}/CMR_{glc}$, where CMR_{glc} is the mean of $rCMR_{glc}$ in corticocerebral gray matter regions, as well as metabolic asymmetry indexes using the following equation:

$$\text{Asymmetry Index}\ (\%) = \frac{R - L}{(R + L)/2} \times 100$$

where R stands for $rCMR_{glc}$ in a right-sided region and L stands for $rCMR_{glc}$ in the homologous region in the left hemisphere.[27,29]

CT Scanning.—Noncontrast CT imaging of the brain was performed with an 8800 CT/T scanner (General Electric Corp, Milwaukee, Wis), for which full width at half maximum equaled 1 mm. Images were obtained parallel to the externally defined inferior orbitomeatal line and were analyzed quantitatively as described previously[31] to obtain volumes (cubic centimeters) for the third and lateral ventricles. Rates of change of ventricular volumes ($cm^3 \cdot y^{-1}$) were calculated from slopes of plots of ventricular volumes against time.

Neuropsychological Testing.—Overall dementia severity was measured using the Mattis Dementia Scale[32] and the full-scale IQ from the Wechsler Adult Intelligence Scale (WAIS).[33] Memory was evaluated with tests of immediate and delayed recall for stories and figures from the Wechsler Memory Scale.[34,35] Ability to maintain attention to complex or shifting sets, and planning ability, were evaluated with the Stroop Color Word Test,[36] the Trailmaking Test,[37] and the Porteus Maze Test.[38] Measures of language were the Verbal Comprehension and Memory and Distractibility Deviation Quotients from the WAIS,[39] a test of comprehension of syntactic relations in single sentences, and a test of serial naming (Controlled Word Association).[40] Measures of visuospatial construction were the WAIS Perceptual Organization Deviation Quotient, a test of the ability to copy geometric features of varying complexity (Extended Range Drawing),[29] and a test of three-dimensional block construction (Hiskey-Nebraska Block Patterns).[41]

For twin pair 1, the control sample was 10 subjects (5 men and 5 women) with a mean age (±SD) of 62 ± 8 years, and a mean education (±SD) of 13 ± 1 years. For twin pair 2, the control sample consisted of 38 men with a mean age of 64 ± 8 years and a mean education of 17 ± 2 years. For twin pair 3, the control sample was 13 women with a mean age of 63 ± 5 years and mean education of 13 ± 1 years. Thus, control subjects for twin pairs 2 and 3 were matched for age, sex, and education, but control subjects for twin pair 1 were not all male and were more educated than the twins.

Molecular Genetic Studies.—The physical structure of the portion of the proximal arm of chromosome 21, which has been suggested to harbor the familial Alzheimer's disease locus,[20,21] was assessed for postzygotic microdeletions or duplications that might discriminate affected from unaffected twins. Equivalent quantities of genomic DNA prepared from buffy coat leukocytes were digested to completion with the restriction enzymes *Eco*RI and *Hin*dIII. The resultant restriction fragments were resolved according to size by horizontal agarose gel electrophoresis and were transferred to nylon membranes by Southern blotting. Radiolabeled probes for the proximal chromosome 21 marker loci D21S11 (pPW236B), D21S52 (pPW511-1H), and D21S13 (pGSM21) then were hybridized to the genomic DNA on the nylon filter supports. The pattern of *Eco*RI and *Hin*dIII sites around these loci was deduced from the size and number of bands on the resultant autoradiogram, and were compared both between affected and unaffected twins, and with the known normal restriction patterns for these enzymes at these loci. At the D21S52 locus, the probe pPW511-1H reveals a restriction fragment length polymorphism with the enzyme *Hin*dIII. In individuals heterozygous for this restriction fragment length polymorphism, the signal from each copy of chromosome 21 can be resolved, and the intensity of the signal contributed by each chromosome can be compared to discover evidence of microduplications.[42] Two twin pairs (3A* and 3B; 2A* and 2B) each were polymorphic for this restriction fragment length polymorphism, having two alleles in each of the twins.

Statistical Analysis.—*Z* scores were used to decide if a particular value in a subject was significantly different from the control mean. A significant *Z* score was defined as 2 SDs above or below the control mean, equivalent to a level of significance of $P < .05$.[43] Mean values (±SD) are presented for control data.

RESULTS

Case Histories and Neuropathology

Twin Pair 1.—The twins 1A* and 1B, born in November 1925 are white men who were raised in rural Arkansas and attended school to the 11th grade. Both worked on a farm for more than 8 years, prior to the age of 30 years, where they were exposed to pesticides handled without gloves or masks. Both then worked in the construction business.

Medical History and Examination.—The twins were born at full-term by uneventful vaginal deliveries, 1A* being born first, and both had uneventful childhoods. Family history for DAT was negative (Fig 1, twin pair 1). In 1978, 1A* evinced personality changes with jealousy and paranoia and lost concern for safety while at work. Memory impairment became obvious in 1980. His medical history includes smoking one to two packs of cigarettes daily for over three decades and exposure to pesticides. His Mini-Mental State Examination (MMSE) scores[44] were 2, 2, and 1 in July 1985, February 1986, and January 1987, respectively, indicative of severe demen-

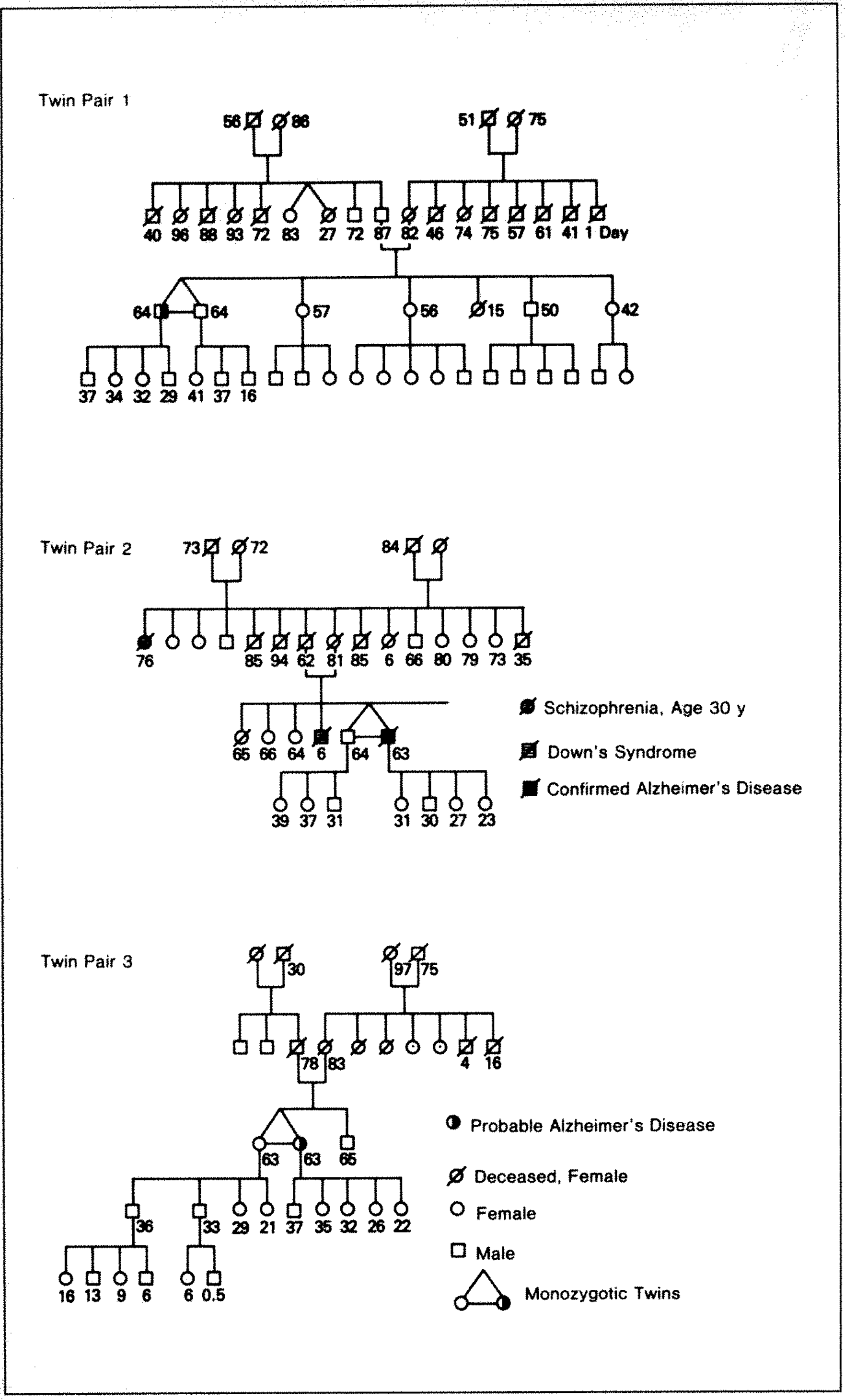

Fig 1.—Dementing illness in twin pair families. There was no evidence of a dementing illness in any family member of each of the affected twins. Half-filled circles and squares represent probable Alzheimer's disease in probands 1A* (twin pair 1) and 3A* (twin pair 3), whereas solid square represents autopsy proved Alzheimer's disease in twin 2A* (twin pair 2). Aunt of twin 2A* was diagnosed as having paranoid schizophrenia at the age of 30 years; a sibling died of Down's syndrome at the age of 6 years.

tia. His Hachinski Ischemic Score equaled 4; a score exceeding 6 suggests multiple infarct disease.[4,5]

Neurological Examination.—In May 1985, twin 1A* appeared alert and cooperative, with marked word-finding difficulty. Upper extremities demonstrated cogwheeling and a fine tremor. Deep tendon reflexes were normal (1+ to 2+ bilaterally), but snout and glabellar reflexes were present. In February 1986, he had no spontaneous speech, with responses limited to a few words. Gait was slow, with bradykinesia and diminished arm swing. In January 1987, he was barely cooperative, with marked cogwheeling of upper extremities and a stooped posture on walking.

The normal twin, 1B, had entirely normal neurological and mental status examination results, with MMSE scores of 26, 29, 25, and 30 in February 1985, February 1986, January 1987, and January 1988, respectively, and a Hachinski Ischemic Score of 4. He had evidence of Raynaud's disease and had a transient ischemic attack in October 1986, but no episode since then.

Twin Pair 2.—Twins 2A* and 2B are white men who were born in June 1925, and were raised in Idaho, where both graduated from high school. After participating in World War II, they returned to Idaho, where each completed 4 years of college. Twin 2A* moved to Montana after he was 30 years old, where he worked as a physical education instructor. Twin 2B worked as an accountant, spending 4 years at a pesticide warehouse, where he may have been exposed to dichlorodiphenyltrichloroethane (DDT) and octachlorotetrahydro - 4,7 - methanoindane (Chlordane). He remains healthy and working.

Medical History and Examination.—Both twins were born by uncomplicated vaginal deliveries, twin 2B being born first. Twin 2A* smoked one pack of cigarettes daily until 1983. The sister of the twins' mother was diagnosed with schizophrenia at the age of 30 years, and that diagnosis was retained until her death (Fig 1, twin pair 2). A brother of the twins had Down's syndrome and died at the age of 6 years. The family history is negative for DAT.

Symptoms in twin 2A* began in 1981; he was diagnosed in 1983 as having DAT. Since he was noted to be hypertensive in 1985, he has been receiving Minipres (prazosin, Pfizer, New York, NY), 2 mg orally daily. In May 1986, he demonstrated mumbling speech with word-finding difficulty and myoclonus. He had cogwheeling of both arms and a diminished arm swing, and he walked with a stooped posture. Reflexes ranged from 1+ to 3+. A grasp reflex was present bilaterally. In July 1987, he displayed prominent dysphasia and was capable only of "yes" and "no" responses. Severe motor apraxia was present. In February 1988, his speech was unintelligible, and he demonstrated glabellar, snout, and grasp reflexes. His MMSE scores were 6, 1, and 0 in September 1985, No-

Table 1. Neuropsychological Test Scores for Affected and Normal Twins at Different Times.

	Twin Pair 1					Twin Pair 2					Twin Pair 3				
	Normal (1B)			Affected (1A*)		Normal (2B)			Affected (2A*)		Normal (3B)			Affected (3A*)	
Neuropsychological Test	**2/85**	**2/86**	**2/87**	**2/85**	**2/86**	**9/85**	**5/86**	**8/87**	**9/85**	**5/86**	**8/85**	**4/86**	**4/87**	**8/85**	**4/86**
Omnibus Scales															
Mattis Dementia Scale	136	143	141	47‡	33‡	142	142	144	76‡	76‡	143	142	142	54‡	30‡
WAIS† Full-Scale IQ	100‡	111	107	52‡	NA	113	103‡	109	63	64	111	117	120	NA	NA
Memory (Wechsler Memory Scale)															
Immediate Story Recall	12	10	17	0‡	NA	14	15	22	NA	NA	10	13	21	NA	NA
Delayed Story Recall	5	9	18	0‡	NA	9	12	19	NA	NA	7	13	18	NA	NA
Immediate Visual Reproduction	3‡	5	5	0‡	NA	10	11	13	NA	NA	8	8	11	NA	NA
Delayed Visual Reproduction	1	5	8	0‡	NA	8	11	9	NA	NA	9	8	11	NA	NA
Attention and Planning															
Stroop Color Word	16‡	30	25	1‡	2‡	NA§	NA	NA	0‡	NA	38	41	39	NA	NA
Trailmaking (trail B, s)	110	111	108	>500‡	NA	81	83	70	NA	NA	52	73	72	NA	NA
Porteus Mazes (test age, y)	12.5	13.0	15.5	4.0‡	4.0‡	13.0	15.5	13.5	NA	NA	15.0	16.5	16.0	NA	NA
Language															
WAIS VDQ	113	117	120	57‡	NA	114	108‡	111	85‡	83‡	108	118	115	NA	NA
WAIS MDQ	91	109	97	48‡	NA	100	91‡	97	62‡	71‡	91	103	106	NA	NA
Syntax Comprehension	21‡	21‡	22	0‡	3‡	18‡	17‡	22	4‡	6‡	26	26	26	NA	NA
Controlled Word Association (VF)	28	28	33	0‡	NA	27	26	34	6‡	11‡	51	40	44	NA	NA
Visuospatial Construction															
WAIS PDQ	89‡	103	92‡	46‡	NA	122	105	108	46‡	46‡	100	114	119	NA	NA
Extended Range Drawing	15	16	15	0‡	0‡	19	22	17	4‡	2‡	16	16	19	8‡	0‡
Hiskey-Nebraska Block Patterns	10	11	8	1‡	NA	14	14	15	NA	NA	8	7	7	NA	NA

*Asterisk denotes the twin with a diagnosis of dementia of Alzheimer's type, probable Alzheimer's disease, using National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Diseases Association criteria.

†WAIS indicates Wechsler Adult Intelligence Scale; VDQ, Verbal Comprehension Deviation Quotient; MDQ, Memory and Distractibility Deviation Quotient; PDQ, Perceptual Organization Deviation Quotient; NA, not administered; and VF, verbal fluency.

‡Differs from control mean by more than 2 SDs ($P < .05$). Different control samples were used for each twin pair. See text for details.

§Twin 2B could not perform the Stroop Color Word due to color blindness.

vember 1986, and February 1988, respectively, indicative of severe dementia, and his Hachinski Ischemic Score equaled 1.

Three measurements of cerebrospinal fluid concentration of homovanillic acid in twin 2A* made between January 1985 and July 1987 ranged from 31 to 50 nmol/L; closer to the mean found for patients with DAT with extrapyramidal signs including myoclonus (60 nmol/L) than to the mean in patients with DAT without extrapyramidal signs or myoclonus (168 nmol/L).[46] Cerebrospinal fluid concentration of 5-hydroxyindoleacetic acid in twin 2A* measured in September 1985 equaled 61.4 nmol/L, close to the mean of 64 nmol/L for patients with DAT with extrapyramidal symptoms and myoclonus, as compared with the mean for patients with DAT without these signs (116 nmol/L).[46]

Neuropathologic Examination.—Twin 2A* died in September 1988, at the age of 63 years. The pathology report by one of us (M.J.B.) was consistent with an unequivocal diagnosis of Alzheimer's disease, with no evidence of Parkinson's disease. The formalin-fixed brain weighed 1080 g. Corticocerebral atrophy was prominent, particularly in the frontal poles. Large numbers of senile (neuritic) plaques, with occasional well-developed amyloid cores, were found throughout the hippocampal formation bilaterally, where the pyramidal cortex showed enormous numbers of neurofibrillary tangles of the Alzheimer's type, granulovacuolar degeneration, and rodlike Hirano bodies. Large numbers of neurofibrillary tangles also were present in the amygdaloid nuclei, where nerve cell loss was prominent. There was no evidence of congophilic angiopathy. Vast numbers of senile plaques were found throughout the left middle-frontal and left inferotemporal gyri, with neurofibrillary tangles particularly prominent in laminae III and V, and neuronal dropout evident. The densities of neuritic plaques and neurofibrillary tangles in the multiple regions sampled fulfilled the quantitative criteria required for a diagnosis of Alzheimer's disease, proposed by a National Institutes of Health panel.[47]

Nerve cells in the striatum were well preserved, as were neuromelanin-pigmented neurons in both the pars compacta and pars reticulata of each substantia nigra. Extensive search failed to reveal a single intracytoplasmic Lewy inclusion body or a neurofibrillary tangle in either substantia nigra. A modest amount of iron was deposited within the nigrostriatal tract.

The normal twin, 2B, has no reported difficulty in any cognitive function. He has essential hypertension and gout, and is on a regimen of prazosin and zyloprim (Burroughs Wellcome, Research Triangle Park, NC). His blood pressure in August 1987 was 162/90 mm Hg. He was neurologically normal on repeated examinations, with a normal mental status and MMSE scores of 29, 29, and 30 in September 1985, May 1986, and October 1986, respectively. His Hachinski Ischemic Score equaled 1. In September 1985, his cerebrospinal fluid concentration levels of homovanillic acid and 5-hydroxyindoleacetic acid equaled 49 nmol/L and 42 nmol/L, respectively.

Twin Pair 3.—Twins 3A* and 3B, born in June 1926, are white women who were raised in Montana. Both attended college for 1 year, before taking teaching jobs. Both women married at the age of 21 and lived in the same neighborhood until twin 3A* moved to a nursing home 3 years ago. There is no positive family history for DAT (Fig 1, twin pair 3).

Medical History.—Both twins were born at term by uncomplicated vaginal delivery; twin 3B was born first. Intellectual decline in twin 3A* started in 1980. She currently resides in a nursing home.

Neurological Examination.—In April 1986, twin 3A* demonstrated absent spontaneous speech and poor understanding of tasks. In April 1987, her tendon reflexes were 1+ to 2+ bilaterally, with down-going plantar reflexes. In February 1988, there was, additionally, a grasp reflex bilaterally. She was found to have carcinoma of the left breast and underwent a successful radical mastectomy. Her MMSE scores in August 1985, August 1986, and February 1988 were 7, 1, and 0, respectively, and her Hachinski Ischemic Score equaled 1.

The unaffected twin, 3B, is a housewife with normal intellectual and social functioning. The results of her medical and neurological examinations were normal, and she obtained the MMSE scores of 30, 29, and 30 in August 1985, April 1986, and April 1987, respectively. Her Hachinski Ischemic Score equaled 0.

Genetic Analysis

The following blood group and histocompatibility (HLA) antigen determinations were made in each twin pair[48]: (1) HLA antigens: A, B, C, DR; (2) blood group antigens: ABO, Rh (C, Cw, D, E, c, e), MNS (M, N, S, s) P (P1), Kell (K, k, Kp^a, Kp^b), Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b), and Lewis (Le^a, Le^b). Each twin pair was found to be monozygous with respect to each of these antigens. From blood group antigen conformity alone, the likelihood of monozygosity in each twin pair was calculated as $P < .00001$.[49]

No difference in the *Eco*R1 or *Hin*dIII restriction patterns was observed between the affected and the normal twin at any of the three chromosome 21 loci examined. Consequently, no evidence against monozygosity was observed, nor was there evidence of a postzygotic structural defect in chromosome 21 in any affected twin.

Cognitive, Neuroanatomic, and Metabolic Measurements

Neuropsychological test scores on initial examination (Table 1) demonstrated that each affected twin was severely demented, as illustrated by the Mattis Dementia Scale score. Test scores were not recorded if the patient could not comply with instructions. Affected twins 1A* and 3A* showed worsening of dementia over the follow-

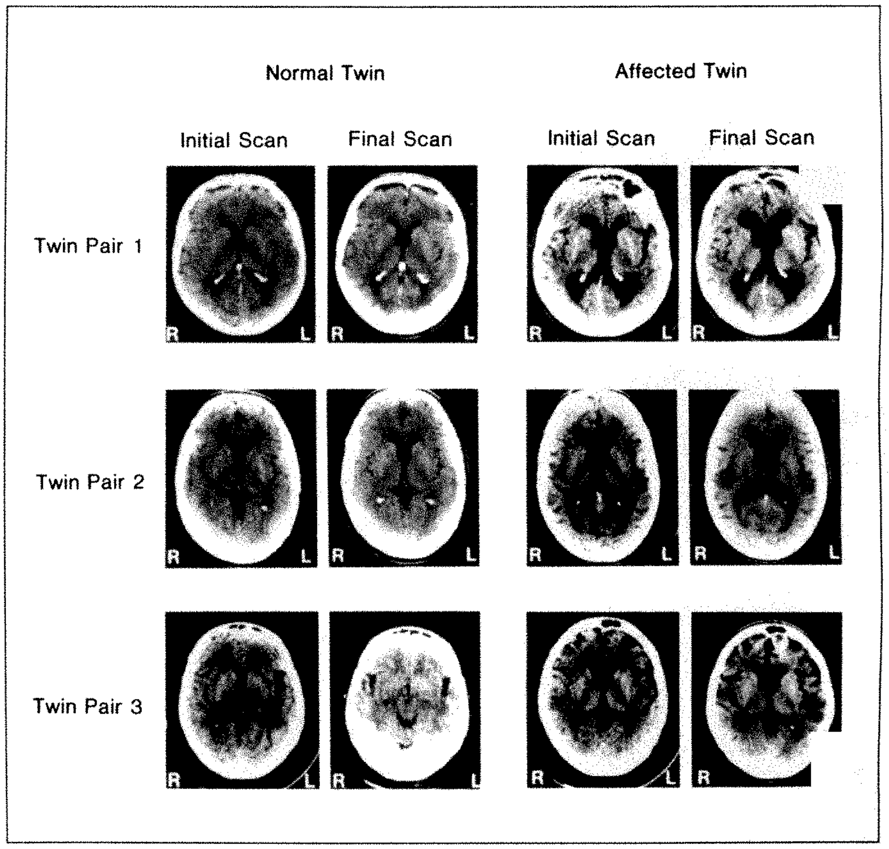

Fig 2.—Initial and final computed tomographic scans of normal and affected twins, at 55 mm above the inferior orbitomeatal line. Computed tomographic scans for twin pair 1 were taken in February 1985 and January 1987 (normal) and in February 1985 and February 1986 (affected); for twin pair 2, in September 1985 and August 1987 (normal) and in September 1985 and June 1987 (affected); and for twin pair 3, in August 1985 and April 1987 (normal) and in May 1985 and April 1987 (affected).

Table 2.—Initial Ventricular Volumes and Rates of Change of Ventricular Volumes in Twin Pairs

	Twin Pair 1		Twin Pair 2		Twin Pair 3		Control Subjects,† mean ± SD	
Region	1A*	1B	2A*	2B	3A*	3B	Men	Women
				Volume, cm^3				
Third ventricle	3.90‡	1.60	5.00‡	2.60	1.60	0.3	1.70 ± 0.74	1.02 ± 0.03
Lateral ventricle								
Left	77.50‡	9.80	35.70	13.30	21.00‡	7.00	18.5 ± 11.8	7.9 ± 5.0
Right	60.90‡	10.70	36.80‡	11.20	15.60	7.50	16.7 ± 9.8	8.8 ± 10.1
Total	138.40‡	20.50	72.50	24.50	36.60	14.50	35.2 ± 21.4	16.0 ± 14.9
				Rate of Volume Change, cm^3/y				
Interval, y	0.70	2.00	1.00	2.00	2.00	1.6	1.63	2.85
Third ventricle	3.46‡	0.30	0.44	−0.39	0.66	0.36	0.22 ± 0.30	0.28 ± 0.46
Lateral ventricle								
Left	−1.10	−0.20	2.41‡	0.09	2.08	. . .	−1.10 ± 1.00	0.76 ± 1.3
Right	−0.8	−0.7	0.80	0.78	3.80‡	. . .	−1.00 ± 0.90	0.30 ± 0.60
Total	−1.90	−0.90	1.60	0.87	5.70	. . .	−2.10 ± 1.89	1.09 ± 2.90

*See footnote to Table 1 for explanation.

†Control subjects include 21 men and 19 women in "Volume" section and 7 men and 4 women in "Rate of Volume Change" section.

‡Differs by 2 SDs from appropriate control mean.

up periods of a year or less, whereas affected twin 2A* did not have lower scores on an 8-month follow-up, but had a reduced Mattis score, of 37, after 29 months (February 1988).

Some initial test scores of normal twin 1B were more than 2 SDs below control means. With one exception (WAIS Perceptual Organization Deviation Quotient), these differences disappeared on subsequent examination. Initial low values may have been due to anxiety, or to the fact that control subjects were more educated than twin 1B (see "Subjects and Methods" section). Some test scores of normal twin 2B also were significantly reduced on initial examination, but on the third (August 1987) and later (March 1988 and March 1990) examinations (not reported in Table 1), cognitive test scores were normal and constant. No test score of normal twin 3B was abnormal, not only at the times noted in Table 1, but in November 1988 as well. No unaffected twin had an abnormal score on the Delayed Story Recall, a test of memory that is characteristically impaired in early DAT.[50-52] Thus, there was no evidence of abnormal or deteriorating cognitive function in normal twins. Function was stable in twin 1B for 2 years, in twin 2B for 5 years, and in twin 3B for more than 3 years.

Figure 2 illustrates initial and final CT scans of normal and affected twins. Whereas ventricular dimensions were read as normal for each unaffected twin, the lateral ventricles in each affected twin were markedly dilated at all times, and severe gyral atrophy was apparent.

Table 2 summarizes volumetric data derived from the CT scans. The net volume of the lateral ventricles of twin 1A* at initial examination equaled 138 cm^3, 6.6 times the mean of 21 cm^3 for age-matched male control subjects, whereas the initial volume of the third ventricle was about twofold higher than the control mean ($P < .05$). The third and right lateral ventricles of twin 2A* and the left lateral ventricle of twin 3A* also were significantly dilated on initial scans. With respect to rates of volume change, the third ventricle of twin 1A*, the left lateral ventricle of twin 2A*, and the right lateral ventricle of twin 3A* dilated more rapidly than in age- and sex-matched control subjects. No abnormal ventricular volume or rate of change of ventricular volume was noted in any unaffected twin (Table 2). Rates of change of lateral ventricular volumes of twin 3B are not given in Table 2 because of the inadequacy of her final CT (Fig 2).

Table 3 summarizes serial $rCMR_{glc}$ values and their ratios to mean gray matter CMR_{glc}, as well as metabolic asymmetries (Equation 1) for each twin. Individual measurements were compared, using a Z-score analysis, with appropriate means for age-, sex-

Table 3.—Serial Analyses of Cerebral Glucose Utilization in Identical Twins*

	Affected Twin			Normal Twin		
Evaluation	**1**	**2**	**3**	**4**	**5**	**6**
			Twin Pair 1			
Date	2/85	2/86	2/87	2/85	2/86	1/88
Scanner	ECAT	ECAT	SCX	ECAT	ECAT	SCX
$rCMR_{glc}$, mg · $100g^{-1}$ · min^{-1} ($rCMR_{glc}/CMR_{glc}$)						
R frontal	3.29† (.92)	2.84† (.92†)	2.73† (.82†)	4.41 (.94)	5.29 (.97)	7.38 (1.0)
L frontal	2.96† (.83†)	2.47† (.80†)	2.44† (.74†)	4.64 (.94)	5.60 (1.03)	7.69 (1.00)
R parietal	3.33 (.93)	2.54† (.82†)	2.43† (.73†)	4.64 (.94)	5.08 (.94)	7.46 (1.01)
L parietal	2.74† (.77†)	2.34† (.75†)	2.30† (.69†)	4.79 (1.02)	5.37 (.99)	8.03 (1.09)
R temporal	3.30† (.92)	2.60† (.84)	3.43 † (1.03)	4.20 (.90)	4.84 (.89)	7.18 (.97)
L temporal	3.19† (.89)	2.13† (.69†)	2.85† (.86)	4.29 (.91)	5.07 (.94)	7.50 (1.02)
R calcarine	4.76	4.13	4.88†	4.58	5.10	7.30
L calcarine	4.66	3.73	4.67†	4.75	5.05	8.30
R sensorimotor	3.58	3.68	3.04†	4.73	5.26	7.61
L sensorimotor	3.57	3.32†	3.56†	4.90	5.75	8.43
R-L asymmetry index, %						
Frontal	10.2†	13.8†	11.1†	−5.1	−5.8	−4.1
Parietal	19.3†	8.2	5.3	−3.1	−5.4	−7.3
Temporal	3.3	20.1†	18.5†	−2.1	−4.4	−4.4
			Twin Pair 2			
Date	11/86			5/86	8/87	
Scanner	SCX			SCX	SCX	
$rCMR_{glc}$, mg · $100g^{-1}$ · min^{-1} ($rCMR_{glc}/CMR_{glc}$)						
R fontal	5.47 (1.18†)			7.65 (1.08)	7.94 (1.05)	
L frontal	5.53 (1.14†)			7.20 (1.02)	7.76 (1.03)	
R parietal	3.01† (.67†)			7.17 (1.02)	7.98 (1.06)	
L parietal	3.08† (.67†)			6.22 (.88)	7.70 (1.02)	
R temporal	3.69† (.81†)			6.95 (.94)	7.16 (.95)	
L temporal	3.80† (.82)			6.45 (.91)	6.93 (.92)	
R calcarine	3.92†			7.91	6.53	
L calcarine	3.75†			8.46	7.68	
R sensorimotor	4.32†			7.42	8.73	
L sensorimotor	4.44†			6.78	8.81	
R-L asymmetry index, %						
Frontal	−1.0			6.0	2.3	
Parietal	−2.3			14.2†	3.5	
Temporal	−3.0			7.5	3.2	
			Twin Pair 3			
Date	4/86			4/86	4/87	3/88
Scanner	ECAT			ECAT	SCX	SCX
$rCMR_{glc}$, mg · $100g^{-1}$ · min^{-1} ($rCMR_{glc}/CMR_{glc}$)						
R frontal	2.52† (.79†)			5.90 (1.00)	7.47 (.92)	9.57 (1.05)
L frontal	2.42† (.75†)			5.70 (1.00)	7.09 (.87)	9.43 (1.03)
R parietal	2.62† (.82†)			5.50 (.97)	10.1 (1.24)	10.1 (1.10)
L parietal	2.37† (.74†)			5.40 (.94)	9.47 (1.16†)	10.1 (1.10)
R temporal	2.20† (.69†)			4.93 (.86)	8.76 (1.08†)	8.82 (.96)
L temporal	2.27† (.71†)			4.91 (.85)	8.57 (1.05†)	8.02 (.87)
R calcarine	4.09†			5.20	9.27	9.69
L calcarine	3.87†			5.21	9.69	9.70
R sensorimotor	3.78†			6.42	8.69	10.18
L sensorimotor	3.55†			5.91	8.53	9.94
R-L asymmetry index, %						
Frontal	4.0			3.0	5.3	1.3
Parietal	10.0†			3.1	6.5	0.26
Temporal	−3.0			0.7	2.2	9.4

*ECAT indicates ECAT II tomograph; SCX, Scanditronix tomograph; $rCMR_{glc}$, regional cerebral metabolic rate for glucose; ($rCMR_{glc}/CMR_{glc}$), regional metabolic rate divided by mean gray matter metabolic rate; R-L asymmetry, difference between $rCMR_{glc}$ values on right and left side, divided by their mean (see Equation 1); R, right; and L, left.

†Differs from sex-, age-, and machine-matched control mean[27-30] by 2 SDs ($P < .05$).

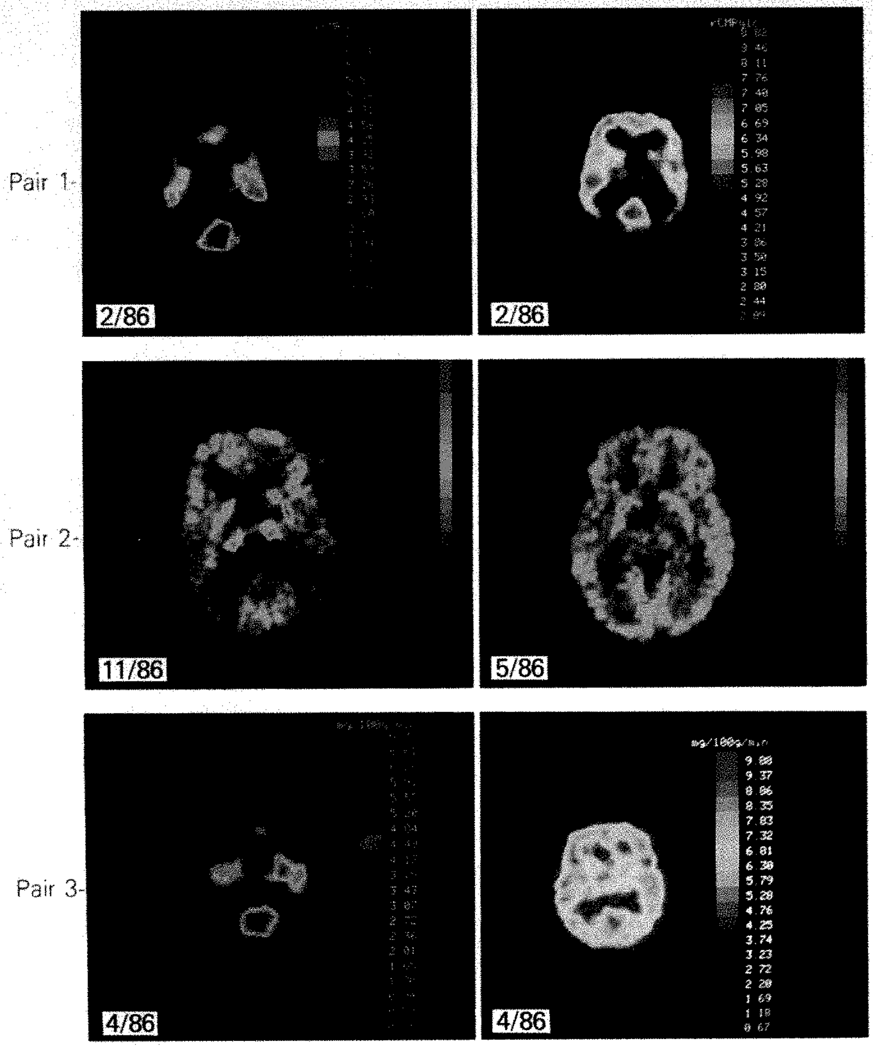

Fig 3.—Positron emission tomographic scans demonstrating cerebral metabolic rates for glucose ($rCMR_{glc}$) in units of $mg \cdot 100\ g^{-1} \cdot min^{-1}$, in affected (left-hand column) and normal (right-hand column) identical twins. Scans are taken at 55 mm above the inferior orbitomeatal line. Scans of twin pairs 1 and 3 are from the ECAT II tomograph, whereas those of twin pair 2 are from the Scanditronix tomograph. Dates of scans are noted in the figure.

and machine-matched control subjects, as reported elsewhere.[27-30] The Scanditronix tomograph provided generally higher recovery rates for $rCMR_{glc}$ than did the ECAT II machine, as described previously.[28]

In each affected twin, most $rCMR_{glc}$ values were more than 2 SDs below the control means ($P < .05$). These reductions also are illustrated in Fig 3. For example, $rCMR_{glc}$ in the right parietal lobe of twin 1A* was 49%, 42%, and 31% of the control mean in his three serial PET scans, and 85%, 74%, and 60% of the control mean in the right calcarine cortex. This decline during 2 years of observation corresponded to declining cognitive test scores (Table 1). The $rCMR_{glc}$ in the right parietal and right calcarine regions of twin 2A* were 39% and 48%, respectively, of the control mean on the first and only scan. For twin 3A*, the $rCMR_{glc}$ values were 46% and 69%, respectively, of the control means. Comparison of data in Table 3 with measurements on patients with DAT by Duara et al[27] shows that each affected twin had $rCMR_{glc}$ values consistent with severe dementia, as measured with the MMSE.

In twin 2A* and twin 3A*, significantly reduced metabolic ratios were apparent in the parietal, temporal and, for twin 3A*, frontal association cortices on the first and only tolerated scans. Twin 1A*, who tolerated three consecutive scans, had consistently reduced metabolic ratios in the frontal and parietal lobes, but not in the temporal lobe.

The metabolic asymmetry index (Equation 1) was unremarkable in twin 2A*, abnormal in the parietal association cortex of twin 3A*, and abnormal in the association cortices in all three scans of twin 1A*. There was no evidence that any PET scan of an unaffected twin showed an abnormal image, except for the initial abnormal metabolic asymmetry index of 2A*, which probably was due to chance. In no unaffected twin was there evidence of worsening of any PET measure.

COMMENT

This study documents discordance of DAT in three twin pairs whose monozygosity was confirmed by extensive HLA and blood group antigen typing. In each twin pair, discordance was demonstrated repeatedly over a period of 2 to 3 years with respect to clinical examination and history, cerebral glucose utilization, and brain ventricular volumes and for 2 to 5 years for neuropsychological test scores. Discordance has been maintained for 11 years in twin pair 1, 8 years in twin pair 2, and 9 years in twin pair 3 (10 years in twin pair 2 and 11 years in twin pair 3 on the basis of cognitive testing alone). No aspect of birth, development, social or medical history, or history of toxic exposure, could distinguish one twin from another, until one developed slowly progressive cognitive impairment diagnosed as DAT.

Postmortem examination of twin 2A* revealed Alzheimer's disease without concurrent Parkinson's disease, even though he had the extrapyramidal signs and myoclonus. This syndrome occurs frequently in moderately to severely demented patients with early onset of DAT, and is accompanied by reduced cerebrospinal levels of homovanillic acid and 5-hydroxyindoleacetic acid.[46] His cerebrospinal fluid profile of these measures was consistent with the group pattern. Absence of neuropathological evidence of Parkinson's disease in twin 2A* indicates that extrapyramidal signs with myoclonus, with cerebrospinal fluid abnormalities, can accompany Alzheimer's disease alone. On the other hand, a recent report[53] indicates that some patients with extrapyramidal signs represent a variant of Alzheimer's disease, with cortical and subcortical Lewy bodies and gross pallor of the substantia nigra.

Twin 2B also had comparatively low levels of cerebrospinal fluid concentrations of homovanillic acid and 5-hydroxyindoleacetic acid. These low values may have been related to his medications.

Although autopsy proofs of Alzheimer's disease in the remaining two affected twins are as yet unavailable, their clinical histories and examinations, together with evidence of worsening cognitive metabolic and anatomic measures and Hachinski Ischemic Scores below 7, make it likely that both had Alzheimer's disease.[23] In our previous studies with this extent of documentation, nine of 10 patients who died with a premorbid diagnosis of DAT (probable Alzheimer's disease, by the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's Disease and Related Diseases Association criteria)[23] were shown on postmortem examination to have had Alzheimer's disease.[51]

In so far as cognitive test scores in the unaffected monozygotic twins provide good estimates of premorbid scores in the affected twins,[54,55] the striking differences in IQ and other cognitive measures between the affected and unaffected twins clearly reflect disease in the affected twins. The test profiles in the affected twins correspond to profiles of severely demented patients with DAT, which are characterized by severe impairment in all tests of memory, language, and cognition.[50]

It is likely that initially reduced cognitive test scores for normal twins 1B and 3B. (Table 1) reflected initial anxiety (as the reductions essentially disappeared on later evaluation), and, for twin 1B, his lower educational status as compared with control subjects. In no unaffected twin was a score abnormal on the Delayed Story Recall test, a memory measure usually affected in early DAT.[50-52] Furthermore, longitudinal reevaluation to date has demonstrated no deterioration in any test score, providing evidence for the absence of a progressive, preclinical disease state in each unaffected twin. This conclusion is consistent with the absence of neuroanatomic and cerebral metabolic evidence of abnormality or of deterioration in any unaffected twin.

Enlarged lateral and third ventricles in the affected twins, and abnormal rates of enlargement of their lateral ventricles, characterize patients with DAT.[56,57] In severely demented patients with DAT, however, markedly enlarged lateral ventricles may not show further enlargement (C. DeCarli, MD, oral communication, January 5, 1990). As illustrated by Table 2, no enlargement of the ventricles in any unaffected twin was noted, nor was there any evidence of acceleration of the rate of enlargement of the ventricles.

Regional abnormalities of absolute values of $rCMR_{glc}$, measured with PET, metabolic asymmetry indexes, and metabolic ratios, are found generally in patients with DAT.[27-29,50,58-60] Such abnormalities were evident in each affected twin. For example, PET measurements in twin 1A* demonstrated abnormalities in the association areas, but not in the sensorimotor or calcarine cortices (Table 3). Involvement of the calcarine and sensorimotor regions, as well as the association areas, in the scans of twins 2A* and 3A* and the later scan of 1A*, is found in patients with severe DAT.[27,30]

No unaffected twin demonstrated a consistent cerebral metabolic abnormality on PET. These results support the discordance of each of the three twin pairs, with respect to the metabolic profile of DAT. They also do not indicate any preclinical or related metabolic abnormality in any discordant twin. Indeed, Fulham et al[61] could not identify any PET-related abnormality in the three at-risk subjects who later developed DAT.

To our knowledge, ours is the only reported study of monozygotic twins said to be discordant for DAT, documented with neuropathology (1 case), proved monozygosity, and detailed neuropsychological testing, PET and quantitative CT. Ours also is the only such study, to our knowledge, in which repeated measures between 2 and 5 years have been gathered. In earlier twin studies by Kallmann[5] and Jarvik et al,[8] monozygosity was not proved and diagnoses of "senile psychosis" and "organic brain syndrome in the senium" were used rather than DAT, according to more critical criteria.[23,62] Of discordant DAT twins said to be monozygotic, explicit documentation by HLA and/or blood group antigen typing was presented only by Hunter et al,[6] Renvoize et al,[13] Zubenko and Ferrell,[15] Resnick et al,[16] and Nee et al[14] (three of 10 twins reported). In these latter studies, postmortem confirmation of Alzheimer's disease was provided only by Hunter et al[6] and Renvoize et al.[13]

The rate of discordance for DAT in monozygotic twins has been estimated as 50% to 60%,[14] entirely from single, cross-sectional reports of discordance. However, as appearance of DAT in a previously unaffected twin may occur even after 11 years of apparent discordance,[15] the absence of longitudinal follow-up in prior reports of discordance makes it likely that the discordance rate for DAT is less than 50%.[19]

Our twins have remained discordant with respect to several sensitive measures of brain function, for between 8 to 11 years (10 to 11 years, if cognitive testing alone is considered). As the longest reported difference in age at onset for DAT in concordant monozygotic twins is 11 years,[15] it is likely that each of our twin pairs truly is discordant. Discordance in monozygotic twins has been reported in some individuals for up to 16 and 20 years,[6,13] strongly suggesting that discordance can exist.

Recent evidence indicates that the proximal region of the q arm of human chromosome 21 contains a familial Alzheimer's disease locus that segregates with the disease phenotype in families with early-onset DAT (H. Orr, MD, personal communication)[20,63,64] (but see Roses et al[65]). We found no indication of a structural defect in the close vicinity (10 to 15 kb) of any of the three DNA loci on the proximal long arm of chromosome 21. None of these markers is very close to the familial Alzheimer's disease locus on chromosome 21. There may be additional familial Alzheimer's disease loci on other chromosomes,[20,65] and our analyses would be insensitive to point mutations. Because of these limitations, discordance in each of the three twin pairs cannot yet be attributed to a nongenetic etiology. Until the familial Alzheimer's disease gene is isolated and available as a probe, we cannot rule out a mutation following cleavage of the embryo, rather than the influence of intrauterine or environmental factors.[66-68]

In conclusion, our data indicate prolonged (8 to 11 years) metabolic, structural, and neuropsychological discordance for DAT in three sets of monozygotic twins. The same measures strongly suggest that each of the affected twins had Alzheimer's disease (confirmed by autopsy in 1 case). The unaffected twins continue to show no sign of decline on serial neuropsychological and other testing.

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References

1. Katzman R. Alzheimer's disease. *N Engl J Med.* 1986;314:964-973.
2. Breitner JCS, Folstein MF. Familial Alzheimer dementia: a prevalent disorder with specific

clinical features. *Psychol Med.* 1984;14:63-80.

3. Mohs RC, Breitner JCS, Silverman JM, Davis KL. Alzheimer's disease: morbid risk among first degree relatives approximates 50% by 90 years of age. *Arch Gen Psychiatry.* 1987;44:405-408.

4. Davidson EA, Robertson EE. Alzheimer's disease with acne rosacea in one of identical twins. *J Neurol Neurosurg Psychiatry.* 1955; 18:72-77.

5. Kallmann FJ. Genetic aspects of mental disorders in later life. In: Kaplan OJ, ed. *Mental Disorders in Later Life,* 2nd ed. Stanford, Calif: Stanford University Press; 1956:26-46.

6. Hunter R, Dayan AD, Wilson J. Alzheimer's disease in one monozygotic twin. *J Neurol Neurosurg Psychiatry.* 1972;35:707-710.

7. Sharman MG, Watt DC, Janota I, Carrasco LH. Alzheimer's disease in a mother and identical twin sons. *Psychol Med.* 1979;9:771-774.

8. Jarvik LF, Ruth V, Matsuyama SS. Organic brain syndrome and aging: a six-year follow-up of surviving twins. *Arch Gen Psychiatry.* 1980; 37:280-286.

9. Cook RH, Schneck SA, Clark DB. Twins with Alzheimer's disease. *Arch Neurol.* 1981;38:300-301.

10. Kilpatrick C, Burns R, Blumbergs P. Identical twins with Alzheimer's disease. *J Neurol Neurosurg Psychiatry.* 1983;46:421-425.

11. Doi A, Fujimoto K, Yoshida M, et al. Alzheimer's disease in identical twin brothers: investigations of their family history and of clinical development of the disease (in Japanese). *Seishin Shinkeigaku Zasshi.* 1984;86:417-447.

12. Embry C, Lippmann S. Presumed Alzheimer's disease beginning at different ages in two twins. *J Am Geriatr Soc.* 1985;33:61-62.

13. Renvoize EB, Mindham RHS, Steward M, McDonald R, Wallace DRD. Identical twins discordant for presenile dementia of the Alzheimer type. *Br J Psychiatry.* 1986;149:509-512.

14. Nee LE, Eldridge R, Sunderland T, et al. Dementia of the Alzheimer type: clinical and family study of 22 twin pairs. *Neurology.* 1987; 37:359-363.

15. Zubenko GS, Ferrell RE. Monozygotic twins concordant for probable Alzheimer disease and increased platelet membrane fluidity. *Am J Med Genet.* 1988;29:431-436.

16. Resnick SM, Gottlieb GL, Gur RE, et al. Identical twins with probable Alzheimer's disease: behavior, anatomy, and physiology. *Neuropsychiatry Neuropsychol Behav Neurol.* 1988; 1:61-72.

17. Fitch N, Becker R, Heller A. The inheritance of Alzheimer's disease: a new interpretation. *Ann Neurol.* 1988;23:14-19.

18. Creasey H, Jorm A, Longley W, Broe GA, Henderson AS. Monozygotic twins discordant for Alzheimer's disease. *Neurology.* 1989;39:1474-1476.

19. Abe K. The morbidity rate and environmental influence in monozygotic co-twins of schizophrenics. *Br J Psychiatry.* 1969;115:519-531.

20. St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science.* 1987;235:885-890.

21. Watkins PC, Watkins PA, Hoffman N, Stanislovitis P. Isolation of single-copy probes detecting DNA polymorphisms from a cosmid library of chromosome 21. *Cytogen Cell Genet.* 1985;40:773-774.

22. Kumar A, Schapiro M, Grady CL, et al. Cerebral metabolic and structural studies in three pairs of identical twin pairs discordant for Alzheimer's disease. *Alzheimer's Dis Rel Disord* 1989; 3(suppl 1):9.

23. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlen E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task force on Alzheimer's disease. *Neurology.* 1984; 34:939-944.

24. Luxenberg JS, May C, Haxby JV, et al. Cerebral metabolism, anatomy, and cognition in monozygotic twins discordant for dementia of the Alzheimer type. *J Neurol Neurosurg Psychiatry.* 1987;50:333-340.

25. Jablon S, Neel JV, Gershowitz H, Atkinson GF. The NAS-NRC twin panel: methods of construction of the panel, zygosity, diagnosis and proposed use. *Am J Hum Genet.* 1967;19:133-161.

26. Duara R, Grady C, Haxby JC, et al. Human brain glucose utilization and cognitive function in relation to age. *Ann Neurol.* 1984;16:702-713.

27. Duara R, Grady C, Haxby JV, et al. Positron emission tomography in Alzheimer's disease. *Neurology.* 1986;36:879-887.

28. Grady CL, Berg G, Carson RE, Daube-Witherspoon ME, Friedland RP, Rapoport SI. Quantitative comparison of cerebral glucose metabolic rates from two positron emission tomographs. *J Nucl Med.* 1989;30:1386-1392.

29. Haxby JV, Duara R, Grady CL, Cutler NR, Rapoport SI. Relations between neuropsychological and cerebral metabolic asymmetries in early Alzheimer's disease. *J Cereb Blood Flow Metab.* 1985;5:193-200.

30. Kumar A, Schapiro MB, Grady C, et al. High resolution studies of cerebral glucose metabolism in Alzheimer's disease. *Neuropsychopharmacology.* In press.

31. Schwartz M, Creasey H, Grady CL, et al. Computed tomographic analysis of brain morphometrics in 30 healthy men, aged 21 to 81 years. *Ann Neurol.* 1985;17:146-157.

32. Mattis S. Mental status examination for organic mental syndrome in the elderly patient. In: Bellack L, Karasu TB, eds. *Geriatric Psychiatry.* New York, NY: Grune & Stratton; 1976:77-121.

33. Wechsler DA. *Wechsler Adult Intelligence Scale.* New York, NY: Psychological Corp; 1955.

34. Wechsler DA. A standardized memory scale for clinical use. *J Psychol.* 1945;19:87-95.

35. Russell EW. A multiple scoring method for the assessment of complex memory functions. *J Consult Clin Psychol.* 1975;43:800-809.

36. Golden CJ. *The Stroop Color and Word Test: A Manual for Clinical and Experimental Uses.* Chicago, Ill: Stoelting, 1978.

37. Reitan RM. Validity of the trail making test as an indicator of organic brain damage. *Percept Mot Skills.* 1958;8:271-276.

38. Porteus SD. *Porteus Maze Test: Fifty Years' Application.* Palo Alto, Calif: Pacific Books; 1965.

39. Tellegen A, Briggs PF. Old wine in new skins: grouping Wechsler subtests into new scales. *J Consult Clin Psychol.* 1967;31:499-506.

40. Benton AL. The measurement of aphasic disorders. In: Vilasquez AC, ed. *Aspectos Patologicos del Langage.* Lima, Peru: Centro Neuropsicologico; 1973.

41. Hiskey MS. Manual: *Hiskey-Nebraska Test of Learning Aptitude.* Lincoln, Neb: College View Printers; 1965.

42. St George-Hyslop PH, Tanzi R, Polinsky RJ. Absence of duplication of chromosome 21 in familial and sporadic Alzheimer's disease. *Science.* 1987;238:664-666.

43. Mendenhall W. *Introduction to Probability and Statistics.* 6th ed. Boston, Mass: PS W Publishers; 1983:45-55.

44. Folstein MF, Folstein SE, McHugh PR. 'Mini Mental State': a practical method for grading the mental state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

45. Hachinski VC, Iliff LD, Zhilka E, et al. Cerebral blood flow in dementia. *Arch Neurol.* 1975;32:632-637.

46. Kaye JA, May C, Atack JR, et al. Cerebrospinal fluid neurochemistry in the myoclonic subtype of Alzheimer's disease. *Ann Neurol.* 1988;24:647-650.

47. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42:1097-1105.

48. Roberts JAF, Pembry ME. *An Introduction to Medical Genetics,* 8th ed. Oxford, England: Oxford University Press; 1985:1-394.

49. Kennedy D, Park RB. Quantitative characters, polygenic inheritance and environmental interactions. In: Cavalli-Sforza LL, Bodmer WF, eds. *The Genetics of Human Populations.* San Francisco, Calif: W. H. Freeman and Co; 1971:570-571.

50. Haxby JV, Grady CL, Duara R, Schlageter N, Berg G, Rapoport SI. Neocortical metabolic abnormalities precede non-memory cognitive deficits in early Alzheimer-type dementia. *Arch Neurol.* 1986;43:882-885.

51. Haxby JV, Grady CL, Koss E, et al. Heterogeneous anterior-posterior metabolic patterns in Alzheimer's type dementia. *Neurology.* 1988; 38:1853-1856.

52. Grady CL, Haxby JV, Horwitz B, et al. Longitudinal study of the early neuropsychological and cerebral metabolic changes in dementia of the Alzheimer type. *J Clin Exp Neuropsychol.* 1988; 10:576-596.

53. Hansen L, Salmon D, Galasko D, et al. The Lewy body variant of Alzheimer's disease: a clinical and pathologic entity. *Neurology.* 1989;40:1-8.

54. Jarvik LF, Kallmann FJ, Falek A. Intellectual changes in aged twins. *J Gerontol.* 1962; 17:289-294.

55. Jarvik LF, Blum JE, Varma AO. Genetic components and intellectual functioning during senescence: a 20 year study of aging twins. *Behav Genet.* 1972;2:159-171.

56. Creasey H, Schwartz M, Frederickson H, Haxby JV, Rapoport SI. Quantitative computed tomography in dementia of the Alzheimer type. *Neurology.* 1986;36:1563-1568.

57. Luxenberg JS, Haxby JV, Sundaram M, Rapoport SI. Rate of ventricular enlargement in dementia of the Alzheimer type correlates with rate of neuropsychological deterioration. *Neurology.* 1987;37:1135-1140.

58. Grady CL, Haxby J, Schapiro M, Kumar A, Friedland R, Rapoport SI. Heterogeneity in dementia of the Alzheimer type (DAT): subgroups identified from cerebral metabolic patterns using positron emission tomography (PET). *Neurology.* 1989;39(suppl 1):167-168.

59. Grady CL, Haxby JV, Schlageter NI, Berg G, Rapoport SI. Stability of metabolic and neuropsychological asymmetries in dementia of the Alzheimer type. *Neurology.* 1986;36:1390-1392.

60. Rapoport SI, Horwitz B, Haxby JV, Grady CL. Alzheimer's disease: metabolic uncoupling of associative brain regions. *Can J Neurol Sci.* 1986; 13(suppl):540-545.

61. Fulham MJ, Polinsky RJ, Nee LE, Baser SM, Brooks RA, Di Chiro G. Cerebral glucose metabolism in dominantly inherited Alzheimer's disease: a longitudinal study. *Neurology.* 1990; 40(suppl 1):150.

62. American Psychiatric Association Task Force on Nomenclature and Statistics. *Diagnostic and Statistical Manual for Mental Disorders, Third edition (DSM III).* Washington, DC: American Psychiatric Association; 1980.

63. Goate AM, Haynes AR, Owen MJ, et al. Predisposing locus for AD on chromosome 21. *Lancet.* 1989;1:352-355.

64. Van Broeckhoven C, Van Hul W, Backhoven SIH, et al. The familial Alzheimer's disease gene is located close to the centromere of chromosome 21. *Am J Hum Genet.* 1988;43:A205.

65. Roses AD, Pericak-Vance MA, Haynes CS, et al. Linkage analysis in late onset familial Alzheimer's disease (AD). *Cytogenet Cell Genet.* 1987;46:684. Abstract.

66. Opitz JM. Some comments on penetrance and related subjects. *Am J Med Genet.* 1981;8:265-274.

67. Kushner BH, Helson L. Monozygotic siblings discordant for neuroblastoma: etiologic implications. *J Pediatr.* 1985;107:405-409.

68. Gericke GS. Genetic and teratological considerations in the analysis of concordant and discordant abnormalities in twins. *S Afr Med J.* 1986;69:111-114.

The Distribution of Cerebral Muscarinic Acetylcholine Receptors In Vivo in Patients With Dementia

A Controlled Study With ^{123}IQNB and Single Photon Emission Computed Tomography

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• A high-affinity muscarinic receptor antagonist, ^{123}IQNB (3-quinuclidinyl-4-iodobenzilate labeled with iodine 123), was used with single photon emission computed tomography to image muscarinic acetylcholine receptors in 14 patients with dementia and in 11 healthy controls. High-resolution single photon emission computed tomographic scanning was performed 21 hours after the intravenous administration of approximately 5 mCi of IQNB. In normal subjects, the images of retained ligand showed a consistent regional pattern that correlated with postmortem studies of the relative distribution of muscarinic receptors in the normal human brain, having high radioactivity counts in the basal ganglia, occipital cortex, and insular cortex, low counts in the thalamus, and virtually no counts in the cerebellum. Eight of 12 patients with a clinical diagnosis of Alzheimer's disease had obvious focal cortical defects in either frontal or posterior temporal cortex. Both patients with a clinical diagnosis of Pick's disease had obvious frontal and anterior temporal defects. A region of interest statistical analysis of relative regional activity revealed a significant reduction bilaterally in the posterior temporal cortex of the patients with Alzheimer's disease compared with controls. This study demonstrates the practicability of acetylcholine receptor imaging with ^{123}IQNB and single photon emission computed tomography. The data suggest that focal abnormalities in muscarinic binding in vivo may characterize some patients with Alzheimer's disease and Pick's disease, but further studies are needed to address questions about partial volume artifacts and receptor quantification.

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A defect in acetylcholinergic neurotransmission is a characteristic feature of Alzheimer's disease (AD). Studies of postmortem tissue[1-10] and of cortical biopsy specimens[6,11-12] from patients with AD have consistently demonstrated reduced markers of presynaptic cholinergic activity. Data about postsynaptic activity, however, have been inconsistent, especially with respect to muscarinic-type cholinergic receptors. While most postmortem studies have not found differences between patients with AD and normal controls in density or affinity of postsynaptic muscarinic receptors,[1,2,5,6,8,13-19] reports of decreased[3,9,20-25] and increased[9,10,26] receptor density have also appeared. The reasons for these discrepancies are uncertain, but they probably involve differences in patient sampling, tissue processing, and assay methodology.[27] Because of such methodological difficulties and the additional possibility that in vivo receptor binding and binding determined in vitro on postmortem tissue may be different,[28,29] the opportunity to study muscarinic receptor binding in vivo in patients with dementia is an important research and clinical agenda.

In 1984, Eckelman et al[30] reported that 3-quinuclidinyl-4-iodobenzilate (IQNB), an iodinated derivative of the high affinity muscarinic receptor antagonist 3-quinuclidinyl benzilate (QNB), could be labeled with iodine 123 and used in conjunction with single photon emission computed tomography (SPECT) to image the distribution of muscarinic receptors in living subjects. They studied one normal individual and one patient with a clinical diagnosis of AD and found in the patient a relative reduction in the retention of the radioactive compound in the left temporoparietal cortex 15 hours after intravenous administration.[31] We report herein our experience

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with ^{123}IQNB and high-resolution SPECT as an approach to studying in vivo the distribution of muscarinic receptors in a larger sample of normal subjects and patients with clinical diagnoses of primary degenerative dementia.

Table 1.—Patient Characteristics*

Patient No./Age, y/Sex	Clinical Diagnosis	Years of Symptoms	Mattis Score†	MRI/CT	IQNB Pattern
1/78/F	AD	5	133	Diffuse atrophy	Bifrontal defect
2/73/F	AD	1	129	Minimal atrophy, greatest in left temporal lobe	Bifrontal defect
3/58/M	AD	4	124	Diffuse atrophy	No obvious focal defects
4/82/M	AD	4	112	Diffuse atrophy	No obvious focal defects
5/65/M	AD	5	109	Diffuse atrophy	No obvious focal defects
6/57/M	AD	4	105	Diffuse atrophy	Left temporoparietal defect
7/80/F	AD	5	98	Minimal diffuse atrophy	No obvious focal deficits
8/58/M	AD	3	97	Diffuse atrophy	Temporoparietal defect, left > right
9/55/M	AD	2.5	97	Diffuse atrophy; ventriculomegaly, right > left	Bilateral temporoparietal defects, right > left
10/49/F	AD	2	92	Severe atrophy, especially in parietal lobes	Bilateral temporoparietal and right frontal defects
11/66/F	AD	7	51	Diffuse atrophy, greater in temporal and parietal lobes	Bilateral temporoparietal defects
12/64/M	AD	5	NA	Severe diffuse atrophy	Bilateral temporoparietal defects
13/57/F	PD	3	94	Frontotemporal atrophy	Bifrontal defect
14/65/M	PD	2	82	Frontotemporal atrophy, left > right	Bifrontal defect

*MRI indicates magnetic resonance imaging; CT, computed tomography; IQNB, 3-quinuclidinyl-4-iodobenzilate; AD, Alzheimer's disease; PD, Pick's disease; and NA, not available.

†From Mattis.[33]

PATIENTS AND METHODS

Patients

Fourteen patients (eight men, six women; mean age, 64.6 years), 12 with a clinical diagnosis of AD and two with a clinical diagnosis of Pick's disease (PD), participated in this study. Each patient had been followed up in the outpatient clinics of the National Institutes of Health, Bethesda, Md, for at least 6 months. Diagnosis was based on *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*, criteria and included a history of gradually progressive intellectual deterioration without focal motor or sensory signs and a laboratory examination that was negative for other significant illnesses. The findings of CT and/or magnetic resonance imaging (MRI) were negative except for signs of generalized atrophy in the patients with AD and frontal-anterior temporal atrophy in the patients thought to have PD. The Hachinski score[32] was less than 4 in each case. The diagnosis of PD was suggested by the presence of frontal lobar atrophy on MRI scan, a history of personality change seemingly out of proportion to the extent of cognitive deterioration, and a profile of neuropsychological deficits suggestive of prominent frontal dysfunction. The Mattis Dementia Scale[33] was administered to each patient prior to the SPECT scan to score general cognitive deficits, which were in the mild to moderate range in most cases. The clinical characteristics of these patients are described in Table 1. Each patient was alert and cooperative at the time of testing, and none was receiving medication with prominent cholinergic effects.

Control Subjects

Eleven normal volunteers (10 men, one woman; mean age, 63.8 years; age range, 42 to 83 years) served as controls. Four control subjects were spouses of patients in the study; the remainder were paid respondents to advertisements in the National Institutes of Health normal volunteer office. Volunteers were carefully screened to exclude individuals with a significant medical and/or psychiatric history and to ensure that they were also medication free. The Mini-Mental State examination[34] was administered at the time of the scan and revealed moderate impairment in two individuals (scores of 19 and 20), both of whom had unremarkable MRI scans and clinical histories, and normal scores in the other subjects (score range, 25 to 29).

Scan Procedure

Iodine 123 was prepared in a cyclotron by the (p,5n) reaction that eliminates contamination with iodine 124. The ^{123}IQNB was synthesized using the Wallach triazene approach, as previously described.[35] Specific activity was determined for each synthesis and averaged 660 Ci/mmol. Each subject received approximately 5 mCi ^{123}IQNB by intravenous injection over a period of 1 to 2 minutes while seated with eyes open. No clinical or subjective effects of the drug were observed. The radiation dosimetry calculated for this dose is 505 mrem to the brain, the organ of maximum exposure after thyroid blockade with Lugol's solution. The subjects remained in the laboratory for approximately 2 hours after administration and then went home.

The subjects came to the scanning room the following day for the SPECT scan. The scan procedure began approximately 21 hours (range, 17 to 24 hours) after injection of the radioligand. The subject was seated in a semireclined position in a comfortable dental chair, which was then raised to bring the head into the scanner gantry. After the head was positioned with external marker lights to set the angle of the slices parallel to, and at set distances from, the canthomeatal line, it was immobilized within the gantry aperture using foam rubber inserts. Most subjects watched a movie on videotape during the procedure to minimize boredom and movement. The scanner is a dedicated head SPECT system (Tomomatic 564, Medimatic Inc, Copenhagen, Denmark) that consists of four detector boxes in a rapidly rotating square array. Each detector box contains 16 sodium iodide scintillation crystals, 25 photomultiplier tubes, and a double-focusing lead collimator.[36] We used a high-resolution collimator that collects four true slices simultaneously (8- to 9-mm resolution [full-width half maximum] in plane, 10 mm thickness, 10-mm gap between slices). After the first scan, the chair was moved down 10 mm, repositioning the head for a second series of slices. This procedure yielded eight contiguous true slices in a total acquisition time of 80 minutes with approximately 750 000 counts per slice. One subject (patient 2) was scanned using a prototype collimator, 6-mm resolution (full-width half maximum) in plane. Images were reconstructed using a standard filtered back projection algorithm that includes attenuation and background corrections.[36] Attenuation correction was performed by the first-order precorrection technique of Kay and Keyes,[37] which utilizes the arithmetic mean of opposing projections. This method employs an attenuation constant and the distance each projection traverses in the attenuating volume to determine the magnitude of the correction factor applied to each projection. We determined the optimum value of the attenuation constant for our scanner configuration empirically, by reconstructing scans of a uniform flood phantom approximating the geometry of the human head and then choosing the value that yielded the most uniform profile for iodine 123. Uniformity and background corrections were applied on a channel-by-channel basis by counting a uniform iodine 123 flood phantom and background count rates immediately prior

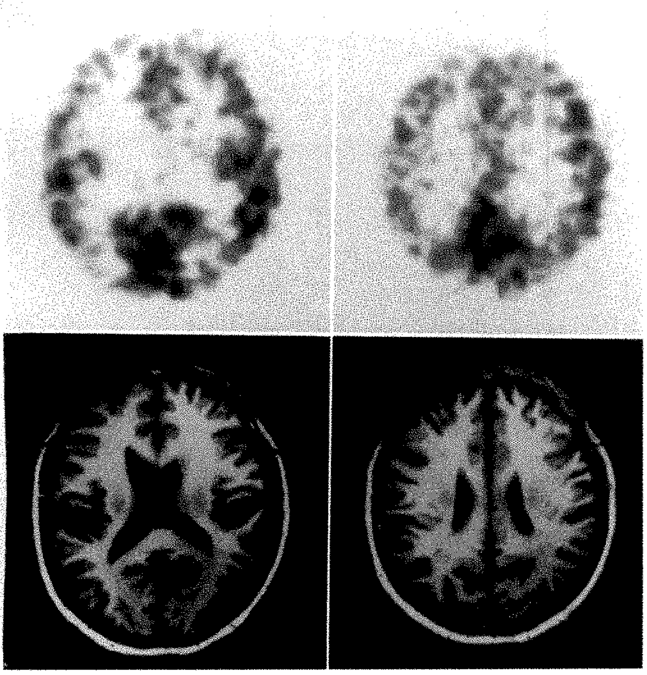


Fig 1.—Iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic images of a normal subject (upper row) and corresponding magnetic resonance imaging scans. Images on the left are cortical slices 20 mm above basal ganglia (BG) level. Images on the right are cortical slices 30 mm above BG level. Left hemisphere is on the left side of the image.

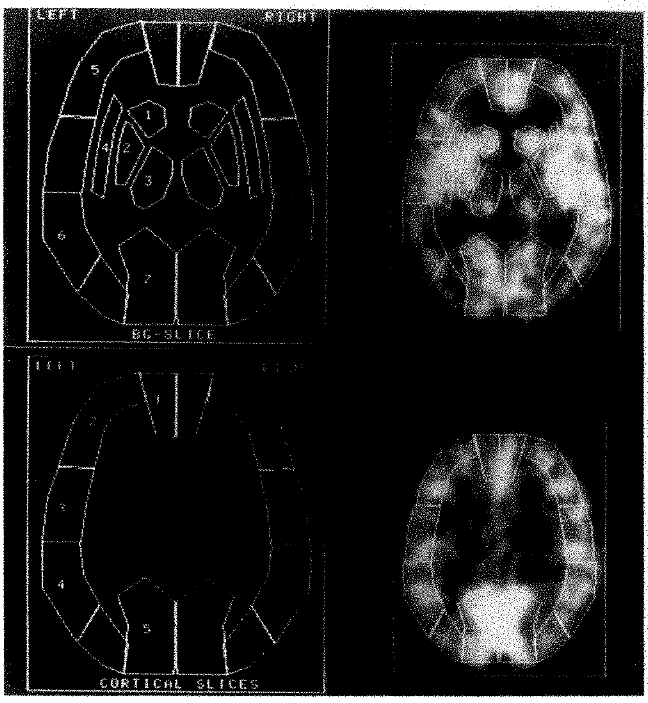


Fig 2.—Region of interest overlay conformed by computer to basal ganglia (BG) slice (upper) and 20-mm cortical slice of iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic images of a normal subject. In the BG slice, 1 corresponds to caudate; 2, putamen; 3, thalamus; 4, insular cortex; 5, frontal cortex; 6, temporal cortex; and 7, occipital cortex. In the cortical slice, 1, medial frontal cortex; 2, lateral frontal; 3, pericentral; 4, temporal; and 5, occipital.

to each scan. Correction was also made for the decay of iodine 123 over the time interval separating the two scan sequences (typically 3% to 4%).

Region of Interest (ROI) Analysis

Based on in vitro autoradiographic data on the distribution of muscarinic receptors in the human brain,[38] and on the results of studies of regional cortical metabolism in patients with AD,[39-43] we selected three SPECT slices for relative distribution analysis: one slice through the basal ganglia (BG), which included caudate and putamen, and two more superior slices through the cortex. The BG slice was determined by referring to the MRI scans (or the CT scans in the case of three patients with AD for whom MRI scans were not available), which included an axial series parallel to the canthomeatal line. In every case, the slice either 30 or 40 mm above the canthomeatal line contained the head of the caudate, putamen, and thalamus. The SPECT slice from the corresponding level for each subject was designated the BG slice for that subject. The SPECT slices 20 and 30 mm above the BG slice were utilized as the superior cortical slices. These slices were usually at the level of the bodies of the lateral ventricles (Fig 1). An anatomically shaped ROI overlay was drawn with a manual cursor using the BG SPECT image from one of the normal subjects as a model (Fig 2). This ROI overlay was then used by computer to generate ROI analyses on each of the slices from each of the subjects. This process involved elastically adapting the ROI overlay to conform to the cortical perimeter of each image. Visual inspection of the images with the ROI overlay in place and of the corresponding MRI or CT images indicated that the elastic adaptation process aligned each of the ROIs with the appropriate anatomical structure as defined by a standard anatomical atlas.[44] From the

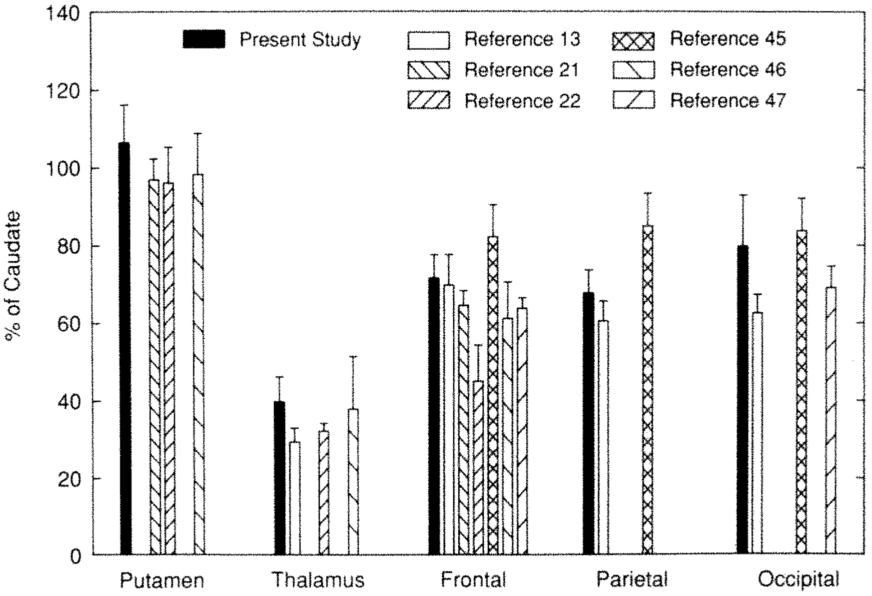
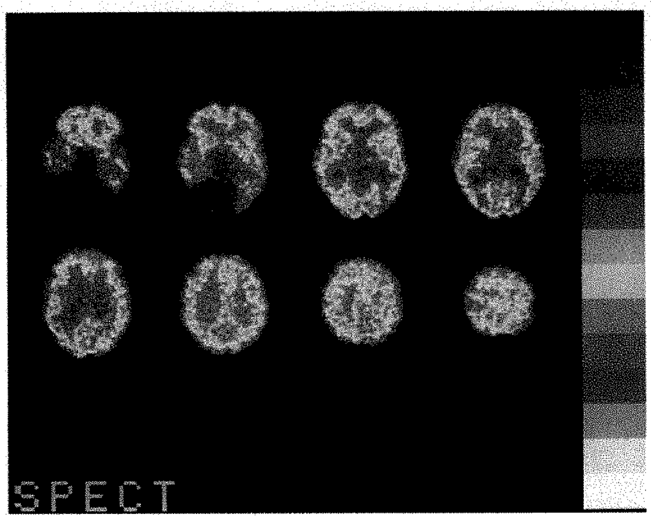
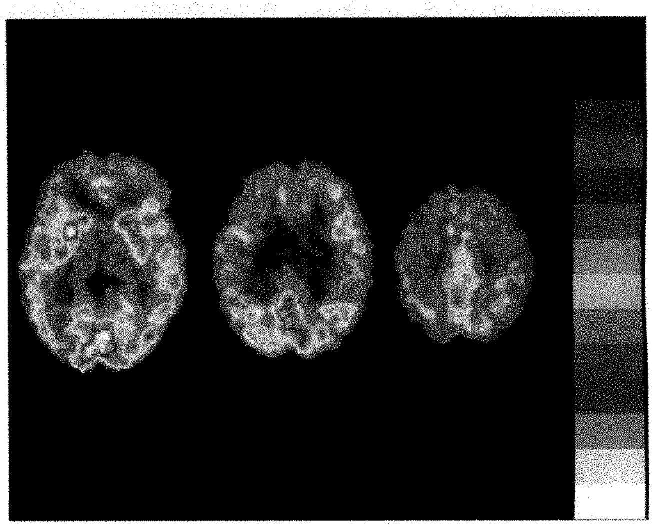


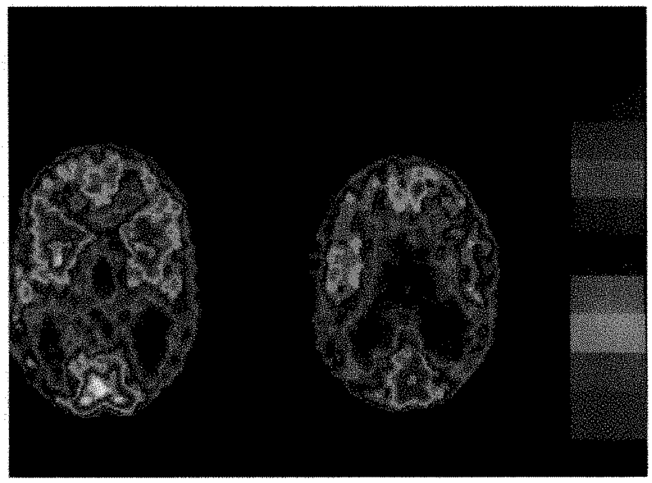
Fig 3.—Comparison of mean (± SD) muscarinic receptor density determined by tritiated QNB radioreceptor assay and iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic data for several brain regions. Tritiated QNB data are taken from in vitro studies in the literature and normalized to caudate (see text).



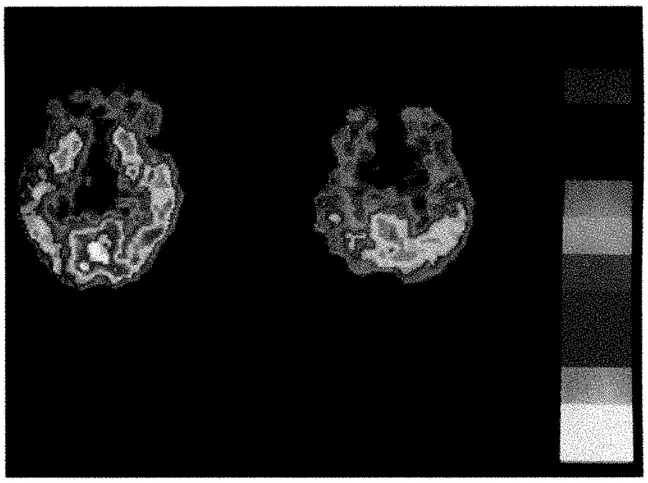
Color Fig 1.—Iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomography (SPECT) series of eight contiguous horizontal slices in a normal subject beginning with a slice through the posterior fossa (upper left) and ending through the superior cortical gray matter (lower right). Color scale is keyed to relative activity (see text), with white corresponding to 100% and darkest blue to 0%.



Color Fig 3.—Patient 2. Iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic images showing frontal defects. This scan was performed with a prototype collimator, 6-mm resolution in plane (full-width half maximum).



Color Fig 2.—Patient 9. Iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic image through basal ganglia and cortical slice showing posterior temporal defects.



Color Fig 4.—Patient 13. Iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic images showing primarily frontal and anterior temporal defects.

BG slice, the following ROIs were analyzed for each hemisphere: caudate, putamen, thalamus, insular cortex, and inferior frontal, lateral temporal, and occipital cortices. From the cortical slice 20 mm above the BG, the following cortical ROIs were analyzed for each hemisphere: medial frontal, lateral frontal, pericentral, posterior temporal, and occipital. From the cortical slice 30 mm above the BG, the following cortical ROIs were analyzed for each hemisphere: medial frontal, lateral frontal, pericentral, posterior temporal/inferior parietal, and occipital. For technical reasons (eg, misalignment or movement), a full set of SPECT slices was not available for every subject. In addition, the scan of patient 2 was excluded from this analysis because it involved higher resolution.

To control for individual differences in injected dose, specific activity, extraction fraction, and postinjection delay time, we adopted a "percent of range" scale for estimation of the relative distribution of retained isotope concentration based on the mean count rate per unit volume from each ROI. This normalization scheme consisted of the following steps: (1) the mean count rate from the ROI with the lowest mean count rate in the full eight slice series was subtracted from all ROIs on the assumption that it represents "noise" (eg, scatter, background, etc); (2) the mean count rate from the ROI with the highest count rate in this same 80-mm-thick brain volume (typically an ROI corresponding to the cuneus of the occipital lobe) was assigned a value of 100%; and (3) the remaining ROIs were proportionately scaled to percentage values in the range of 0% to 100%.

A two-tailed *t* test was used to examine ROI differences between patients with AD and controls. Because of the multiple comparisons, we selected an α value of .01.

Comparison With In Vitro Studies

To examine the similarity between the relative distribution of ^{123}IQNB in vivo and the relative distribution of muscarinic receptors in the *normal* human brain as determined by tritiated QNB in vitro radioreceptor assay, we identified six postmortem studies[13,21,22,45-47] in the literature that provided receptor density data about several comparable brain areas. For each study, absolute receptor densities from the *normal* control group were converted to relative density by dividing the mean density value for a particular structure by the value for the caudate and then multiplying by 100. A similar scaling procedure was applied to the ROI data from our *control* SPECT images.

RESULTS

Control Subjects

Detailed images with high contrast between gray and white matter were acquired in all subjects (Figs 1 and 2 and color Fig 1). A consistent pattern of cerebral retention of the radioligand was seen in the control subjects. This included highest counts in the BG, insular cortex, and occipital cortex; a fairly even distribution in the rest of the cortex; and relatively low counts in the thalamus. Images through the posterior fossa revealed virtually no counts above background in the cerebellum.

Comparison With In Vitro Studies

Figure 3 illustrates the comparison of the relative distribution of ^{123}IQNB in vivo with muscarinic receptor density in vitro in normal controls. In Fig 5, the relative receptor density in vitro from the various studies is plotted for several brain regions against the relative distribution of IQNB in the scans, illustrating the consistency of the relative regional differences. It is apparent from these figures that there is striking similarity between the data from our in vivo studies and the postmortem data.

Patients With Dementia

In 10 of the 14 patients with dementia, visually obvious cortical irregularities in the distribution of ligand were seen usually in several contiguous slices. The most common pattern in the patients with AD was focal defects in posterior temporal-inferior parietal cortex (five patients, see Table 1 and color Fig 2), which was asymmetric in two patients. Three of the patients with AD had focal defects in frontal cortex (color Fig 3); one of these three also had temporoparietal defects. While these defects tended to correspond to areas of relatively greater atrophy on MRI scan in four cases, they did not in four other cases (see Table 1). The pattern of atrophy on the MRI scans was based on neuroradiologists' interpretations of the scans, which were made blind to the SPECT results. Both of the patients with the clinical diagnosis of PD had dramatic reductions in prefrontal and anterior temporal activity (color Fig 4). In the remaining four patients, no unequivocal focal areas of low activity were seen on visual inspection of the scans.

The results of the ROI analysis are shown in Table 2. As discussed above, several subjects were not included in this analysis. The results indicate that the relative distribution of ^{123}IQNB

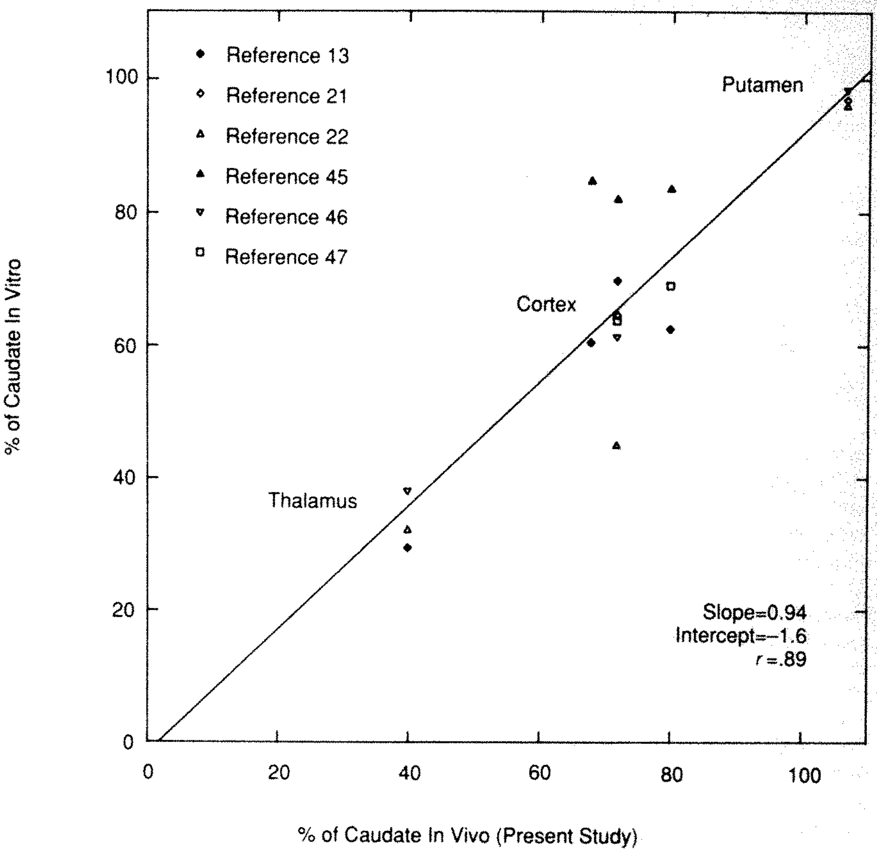


Fig 4.—Plot of mean relative muscarinic receptor density from in vitro studies in the literature as a function of relative iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate single photon emission tomographic data for several brain regions, showing consistent interregional relationships across studies.

Table 2.—Comparison of IQNB Percent of Range Mean (± SD) ROI Values in Patients With Alzheimer's Disease and in Normal Controls*

	Left Hemisphere			Right Hemisphere		
Brain Level/ROI	Patients (n = 8)	Controls (n = 9)	P	Patients (n = 8)	Controls (n = 9)	P
BG slice						
Caudate	56.1 (23.2)	65.6 (15.0)	NS	57.3 (29.4)	63.5 (14.5)	NS
Putamen	80.9 (12.2)	78.8 (18.8)	NS	76.4 (14.8)	77.5 (19.4)	NS
Thalamus	28.9 (10.7)	29.2 (14.5)	NS	31.2 (12.1)	29.3 (13.4)	NS
Insular cortex	79.0 (10.0)	76.0 (16.1)	NS	79.1 (13.7)	82.2 (9.6)	NS
Frontal	50.5 (18.2)	48.9 (11.7)	NS	58.1 (19.6)	57.2 (13.2)	NS
Temporal	46.0 (14.8)	43.9 (10.8)	NS	49.4 (13.0)†	62.6 (9.5)	.03
Occipital	69.8 (22.7)	57.0 (28.3)	NS	70.6 (236)	60.2 (27.7)	NS
	(n = 9)	(n = 9)		(n = 9)	(n = 9)	
BG + 20 mm						
Medial frontal	54.9 (15.6)	54.6 (10.3)	NS	53.9 (10.3)	56.4 (11.9)	NS
Lateral frontal	37.1 (12.0)	44.5 (11.7)	NS	47.6 (15.8)	49.5 (12.3)	NS
Pericentral	56.5 (12.4)	59.9 (10.9)	NS	58.3 (14.5)	63.9 (11.3)	NS
Temporal	36.2 (16.3)	54.8 (11.2)	.01	37.6 (19.3)	63.1 (15.6)	.007
Occipital	72.7 (19.3)	85.3 (9.7)	NS	77.4 (21.6)	88.7 (10.6)	NS
	(n = 9)	(n = 10)		(n = 9)	(n = 10)	
BG + 30 mm						
Medial frontal	57.6 (16.9)	49.2 (11.8)	NS	52.7 (19.6)	49.0 (14.3)	NS
Lateral frontal	36.3 (15.5)	39.0 (14.5)	NS	44.9 (14.5)	42.2 (16.0)	NS
Pericentral	54.9 (13.9)	57.5 (9.3)	NS	57.1 (13.1)	64.7 (13.1)	NS
Posterior temporal/ inferior parietal	33.8 (14.5)	47.2 (11.2)	.04	36.6 (17.4)	52.2 (10.7)	.03
Occipital	70.1 (22.6)	81.1 (10.5)	.09	73.7 (22.6)	84.2 (10.2)	NS

*IQNB indicates 3-quinuclidinyl-4-iodobenzilate; ROI, region of interest; BG, basal ganglia; and NS, not significant.

was significantly different for patients with AD and controls in the posterior temporal cortex bilaterally, but not in other regions. Moreover, activity in right posterior temporal cortex was significantly greater than in the left posterior temporal cortex in normals ($t = 2.7$; $P < .03$; matched-pair t test). This asymmetry was not found in the patients with AD.

COMMENT

We have found that ^{123}IQNB is a practical agent for producing high-contrast, high-resolution images of the brain with SPECT. The compound is relatively easy to synthesize and administer; it is well tolerated and involves low-radiation dosimetry and because it is not retained by white matter, the delayed scans have unusually good gray/white matter contrast. In animal studies, IQNB has been shown to be a high-affinity ligand for muscarinic acetylcholine receptors.[48,49] Therefore, one might assume that the images with this agent at extended times postinjection represent the distribution of these receptors. This assumption is supported by the good correlation between the relative distribution of QNB in the normal SPECT scans and the relative distribution of muscarinic receptors in postmortem in vitro binding studies found in the literature. The results of our study also suggest that many patients with primary degenerative dementia may have qualitatively abnormal IQNB SPECT scans. Before considering the possibility that this represents a muscarinic receptor abnormality, several methodological issues will be addressed.

The pharmacological characteristics of IQNB binding in humans have not been systematically investigated. To our knowledge, saturation binding, ligand competition, and stereospecificity studies have not been performed. Therefore, it is presently unconfirmed that this ligand behaves in humans as it does in rats, in which these complimentary studies have been carried out and in which the receptor binding characteristics and peripheral metabolism of IQNB have been well characterized.[48,49] Even if IQNB functions as a muscarinic receptor ligand in humans, it is still possible that its uptake and retention are primarily dependent on blood flow and that the images may reflect blood flow more than receptor distribution. Indeed, the regional patterns of cortical IQNB defects seen in the patients with dementia are similar to those seen with blood flow tracers and SPECT[50-52] and with blood flow and metabolism tracers with positron emission tomography.[39-43]

On the basis of these uncertainties, it could be argued that the IQNB SPECT data provide information primarily about regional cerebral blood flow (rCBF) and that identical information could be acquired with SPECT and rCBF tracers such as iodoamphetamine[50-53] and ^{99m}Tc-HM-PAO.[54-56] We do not believe that this conclusion is correct. In certain brain regions, there was a dramatic dissociation of rCBF and ligand retention at 21 hours. For example, the delayed scans through the posterior fossa showed virtually no radioligand in the cerebellum, which is consistent with the low density of muscarinic receptors in this region[38] but inconsistent with the fact that blood flow to the cerebellum is relatively high.[57] Similarly, retention of radioligand in the thalamus was relatively much lower than in the BG and the cortex, which is consistent with the relative density of muscarinic receptors[38] but not with blood flow in this region.[58] The possibility that low count rate in the thalamus is an artifact of improper attenuation correction is unlikely because this error would have affected the BG as well. Moreover, our preliminary experience in a small group of patients who have undergone both IQNB SPECT and ^{18}F-2-deoxy-2-fluoro-D-glucose positron emission tomography suggests that rCBF, to the extent that it is coupled with regional glucose metabolism, does not adequately account for the IQNB data.[59] Ultimately, to assess the relative contribution of blood flow and specific receptor binding to IQNB images, detailed analyses of uptake and washout characteristics in vivo are required. Judgment on this issue, therefore, must remain reserved until these studies are performed.

It has recently been shown, using molecular genetic techniques, that at least five subtypes of muscarinic receptors exist in the brain.[60] An older, pharmacologically based subclassification scheme has been used to characterize two receptor subtypes, the so-called M1 and M2 receptors.[60,61] It is uncertain which muscarinic receptor subpopulation is labeled with IQNB in vivo. The pattern of distribution in the delayed scans is similar to the distribution of tritiated QNB binding in postmortem studies (Figs 4 and 5). Tritiated QNB binds with high affinity to both M1 and M2 sites.[62] Nevertheless, animal studies suggest that IQNB and tritiated QNB exhibit some differences in receptor kinetics. In vivo binding data in the rat indicate that the dissociation rate constant of IQNB at the M2 receptor is approximately 16 times faster than at the M1 receptor, even though the affinity of IQNB for both receptor subtypes is similar.[48] This difference in dissociation kinetics could account for washout of the tracer predominantly from M2 sites (eg, thalamus) during the 21-hour period from the administration of ligand to the scan. Our preliminary experience with kinetic studies in monkeys (unpublished observations) suggests that washout of radioligand from the thalamus occurs over several hours, which is consistent with the in vivo binding data in the rat.

An unexpected finding in the normal subjects was a lateralized asymmetry in ^{123}IQNB retention in temporal cortex. To our knowledge, this finding has not been reported in postmortem study of normal subjects, perhaps because both hemispheres have not been assayed in the same samples. We did not find this asymmetry in the patients with AD, which is consistent with a postmortem study that assayed regions of both hemispheres in a similar patient population.[63]

The majority of the patients with dementia had qualitatively abnormal scans, characterized by focal areas of relatively reduced retention of radioligand. If this finding primarily reflects receptor binding rather than rCBF, its interpretation is still not straightforward. Despite efforts to develop a model for quantification of muscarinic receptor affinity and density that could be applied to the SPECT data,[64] to our knowledge a satisfactory model does not yet exist. Therefore, it is unknown whether the scan differences between patients and control subjects represent a change in absolute affinity and/or number of muscarinic receptors. For example, it is uncertain whether focal pattern defects represent areas of reduced binding or of normal binding in a brain where other areas are upregulated. Moreover, in the patients who do not have focal defects on the scans, the possibility that they may have widespread but evenly distributed receptor changes cannot be addressed. These caveats notwithstanding, we agree with Di Chiro and Brooks,[65] who emphasized the potential importance of qualitative imaging data, even without absolute quantification.

Several explanations could account for the pattern of focal defects observed in the scans of the patients with dementia. One possibility is that the patients have focal areas of reduced muscarinic receptor density, perhaps because of degenerative changes in the neural tissue on which these receptors reside. This interpretation is intuitively appealing because muscarinic receptors in the cortex appear to reside on large neurons,[8,16,66,67] and this population of cortical neurons is preferentially lost in AD.[68] This interpretation would be consistent with the lack of clinical benefit of muscarinic receptor agonist drugs.[69] Unfortunately, this explanation is inconsistent with the majority of postmortem in vitro binding studies, which have not found areas of reduced muscarinic receptor density.[1,2,5,6,8,13-19] Nevertheless, the data from ^{123}IQNB and SPECT and the postmortem literature in *diseased* individuals are not readily comparable. Patients in the postmortem studies usually were more severely affected, and binding assays in the postmortem studies tend to be performed on very small tissue samples from only a few discrete brain regions. In fact, only two studies reported receptor density in the parietal cortex,[2,13] and it is uncertain whether any study assayed samples from the posterior temporal cortex. Inconsistencies in the in vivo and the postmortem data may also reflect aspects of functional receptor activity that are apparent only in vivo, a possibility that is becoming increasingly recognized in a variety of receptor systems, especially under pathologic circumstances.[28,29] Whether this possibility exists for muscarinic receptors is unknown. It is interesting to note that in contrast to the postmortem studies of AD, the few examples of muscarinic receptor data in patients with PD described reductions in frontal cortex,[2,70] similar to the relative reduction observed in the scans of our two patients with PD.

Another possibility for the pattern of defects in the patients with AD is that the regional findings actually represent areas of normal receptor number and that the other areas, especially those not typically involved in the neuropathologic changes of AD, such as occipital cortex and BG, are regions in which increased muscarinic receptor density results from upregulation in response to cholinergic deafferentation. The possibility that the failure to find decreased muscarinic receptor density in postmortem studies is caused by compensatory upregulation of preserved receptor domains has been raised by several investigators.[2,5,9,13,16,71] Studies of the behavioral effects of muscarinic agonists in patients with AD have suggested hypersensitivity to some of the effects of these drugs.[71] Nevertheless, most of the postmortem studies, even those that assayed relatively nonpathologic sites such as caudate and occipital cortex, did not find evidence of significant receptor upregulation.

A third possibility is that the finding of focal defects in apparent relative binding is the result of a methodological artifact that complicates tomographic scanning of degenerative brain disorders. Because of brain atrophy and loss of tissue volume, volume elements that comprise the image ("voxels") may have reduced radioactivity counts due to inclusion of enlarged cerebrospinal fluid spaces, even though the actual receptor number per volume of tissue is normal (the so-called partial volume artifact).[72] We cannot rule out that this possibility accounts for some of the focal defects. However, we doubt that it explains them all. Areas of focal atrophy corresponding exclusively to areas of relatively reduced radioactive signal were only occasionally apparent on the CT/MRI scans of the patients. Since atrophy tends to be more diffuse than focal in AD, and since all ROI mean counts were normalized to a relatively nonpathologic region (usually occipital cortex), we would have expected a more widespread pattern of relatively reduced cortical "binding" if atrophy-related partial volume artifact accounted for the data. By the same reasoning, we would have expected occipital binding to have been "relatively" greater in the patients than in the controls. In fact, in most cortical regions, the QNB data did not differ from normal, despite widespread cortical volume loss on the MRI/CT scans. In our experience with another tomographic technique (positron emission tomography) in some of the same patients, the pattern of distribution of activity differed considerably in some cases,[59] which would not have been expected if partial volume phenomena alone accounted for the patterns.

In conclusion, high-resolution images of the retention of a muscarinic acetylcholine receptor ligand in the human brain can be achieved in essentially routine clinical practice with SPECT imaging and ^{123}IQNB. It is likely that the images reflect the distribution of the relative density of a subpopulation of muscarinic receptors. The majority of the patients with primary degenerative dementia had qualitatively abnormal IQNB SPECT scans, perhaps because of focal areas of reduced receptor density. This possibility and the potential clinical utility of this technique will remain uncertain until further studies are conducted and possibly until an in vivo model for quantification of receptor density and affinity with this ligand is developed.

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References

1. Perry EK, Perry RH, Blessed G, Tomlinson BE. Necropsy evidence of central cholinergic deficits in senile dementia. *Lancet.* 1977;1:189.
2. White P, Goodhardt MJ, Keet JP, et al. Neocortical cholinergic neurons in elderly people. *Lancet.* 1977;1:668-671.
3. Reisine TD, Yamamura HI, Bird ED, Spokes E, Enna SJ. Pre- and postsynaptic neurochemical alterations in Alzheimer's disease. *Brain Res.* 1978;159:477-481.
4. Rossor MN, Garrett NJ, Johnson AL, Mountjoy CQ, Roth M, Iversen LL. A post-mortem study of the cholinergic and GABA systems in senile dementia. *Brain.* 1982;105:313-330.
5. Nordberg A, Larsson C, Adolfsson R, Alafuzoff I, Winblad B. Muscarinic receptor compensation in hippocampus of Alzheimer patients. *J Neural Transm.* 1983;56:13-19.
6. Bowen DM, Allen SJ, Benton JS, et al. Biochemical assessment of serotonergic and cholinergic dysfunction and cerebral atrophy in Alzheimer's disease. *J Neurochem.* 1983;41:266-272.
7. Bird TD, Stranahan S, Sumi SM, Raskind M. Alzheimer's disease: choline acetyltransferase activity in brain tissue from clinical and pathological subgroups. *Ann Neurol.* 1983;14:284-293.
8. DeKosky ST, Scheff SW, Markesbery WR. Laminar organization of cholinergic circuits in human frontal cortex in Alzheimer's disease and aging. *Neurology.* 1985;35:1425-1431.
9. London ED, Waller SB. Relationships between choline acetyltransferase and muscarinic binding in aging rodent brain and in Alzheimer's disease. In: Hanin I, ed. *Dynamics of Cholinergic Function.* New York, NY: Plenum Publishing Corp; 1986:215-224.
10. Nordberg A, Nyberg P, Adolfsson R, Winblad B. Cholinergic topography in Alzheimer brains: a comparison with changes in the monoaminergic profile. *J Neural Transm.* 1987;69:19-32.
11. Sims NR, Smith CCT, Davison AN, et al. Glucose metabolism and acetylcholine synthesis in relation to neuronal activity in Alzheimer's disease. *Lancet.* 1980;1:333-336.
12. Francis PT, Palmer AM, Sims NR, et al. Neurochemical studies of early-onset Alzheimer's disease. *N Engl J Med.* 1985;313:7-11.
13. Davies P, Verth AH. Regional distribution of muscarinic acetylcholine receptor in normal and Alzheimer's-type dementia brains. *Brain Res.* 1978;138:385-392.
14. Caulfield MP, Straughan DW, Cross AJ, Crow T, Birdsall NJM. Cortical muscarinic receptor subtypes and Alzheimer's disease. *Lancet.* 1982;2:1277.

15. Palacios JM. Autoradiographic localization of muscarinic cholinergic receptors in the hippocampus of patients with senile dementia. *Brain Res.* 1982;243:173-175.

16. Lang W, Henke H. Cholinergic receptor binding and autoradiography in brains of nonneurological and senile dementia of Alzheimer-type patients. *Brain Res.* 1983;267:271-280.

17. Jenni-Eiermann S, von Hahn HP, Gonegger CG, Ulrich J. Studies on neurotransmitter binding in senile dementia. *Gerontology.* 1984;30:350-358.

18. D'Amato RJ, Zweig RM, Whitehouse PJ, et al. Aminergic systems in Alzheimer's disease and Parkinson's disease. *Ann Neurol.* 1987;22:229-236.

19. Kellar KJ, Whitehouse PJ, Martino-Barrows AM, Marcus K, Price DL. Muscarinic and nicotinic cholinergic binding sites in Alzheimer's disease cerebral cortex. *Brain Res.* 1987;436:62-68.

20. Mash DC, Flynn DD, Potter LT. Loss of M2 muscarinic receptors in the cerebral cortex in Alzheimer's disease and experimental cholinergic denervation. *Science.* 1985;228:1115-1117.

21. Rinne JO, Laakso K, Lönnberg P, et al. Brain muscarinic receptors in senile dementia. *Brain Res.* 1985;336:19-25.

22. Shimohama S, Taniguchi T, Fujiwara M, Kameyama M. Changes in nicotinic and muscarinic cholinergic receptors in Alzheimer-type dementia. *J Neurochem.* 1986;46:288-293.

23. Nordberg A, Alafuzoff I, Winblad B. Muscarinic receptor subtypes in hippocampus in Alzheimer's disease and mixed dementia type. *Neurosci Lett.* 1986;70:160-164.

24. Reinikainen KJ, Riekkinen PJ, Halonen T, Laakso M. Decreased muscarinic receptor binding in cerebral cortex and hippocampus in Alzheimer's disease. *Life Sci.* 1987;41:453-461.

25. Smith CJ, Perry EK, Perry RH, et al. Muscarinic cholinergic receptor subtypes in hippocampus in human cognitive disorders. *J Neurochem.* 1988;50:847-856.

26. Waller SB, Ball MJ, Reynolds MA, London ED. Muscarinic binding and choline acetyltransferase in postmortem brain of demented patients. *Can J Neurol Sci.* 1986;13:528-532.

27. Whitehouse PJ, Au KS. Cholinergic receptors in aging and Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry.* 1986;16:665-676.

28. Bennett Jr JP, Wooten F. Dopamine denervation does not alter in vivo ^{3}H-spiperone binding in rat striatum: implications for external imaging of dopamine receptors in Parkinson's disease. *Ann Neurol.* 1986;19:378-383.

29. Weizman R, Weizman A, Kook KA, Vocci F, Deutsch SI, Paul SM. Repeated swim stress alters brain benzodiazepine receptors measured *in vivo. J Pharmacol Exp Ther.* 1989;249:701-707.

30. Eckelman WC, Reba RC, Rzeszotarski WJ, et al. External imaging of cerebral muscarinic: acetylcholine receptors. *Science.* 1984;223:291-292.

31. Holman BL, Gibson RE, Hill TC, Eckelman WC, Albert M, Reba RC. Muscarinic acetylcholine receptors in Alzheimer's disease: in vivo imaging with iodine 123-labeled 3-quinuclidinyl-4-iodobenzilate and emission tomography. *JAMA.* 1985;254:3063-3066.

32. Hachinski VC, Iliff LD, Zilkha E, et al. Cerebral blood flow in dementia. *Arch Neurol.* 1975;32:632-637.

33. Mattis S. *Dementia Rating Scale Psychological Assessment Resource.* Odessa, Fla: Psychological Assessment Resources Inc; 1988.

34. Folstein MF, Folstein SE, McHuch PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiat Res.* 1975;12:189-198.

35. Rzeszotarski WJ, Eckelman WC, Francis BE, et al. Synthesis and evaluation of radioiodinated derivatives of 1-azabicyclo[2.2.2]oct-3-yl α-hydroxy-α-(4-iodophenyl)-α-phenylacetate as potential radiopharmaceuticals. *J Med Chem.* 1984;27:156-160.

36. Stokely EM, Sveinsdottir E, Lassen NA, Rommer P. A single photon dynamic computer assisted tomograph (DCAT) for imaging brain function in multiple cross sections. *J Comput Assist Tomogr.* 1980;4:230-240.

37. Kay DB, Keyes JW. First order correction for absorption and resolution compensation in radionuclide Fourier tomography. *J Nucl Med.* 1975;16:540-541.

38. Cortés R, Probst A, Tobler HJ, Palacios JM. Muscarinic cholinergic receptor subtypes in the human brain, II: quantitative autoradiographic studies. *Brain Res.* 1986;362:239-253.

39. Frackowiak RSJ, Pozzilli C, Legg NJ, et al. Regional cerebral oxygen supply and utilization in dementia: a clinical and physiological study with oxygen-15 and positron tomography. *Brain.* 1981;104:753-778.

40. Friedland RP, Budinger TF, Ganz E, et al. Regional cerebral metabolic alterations in dementia of the Alzheimer type: positron emission tomography with [^{18}F]fluorodeoxyglucose. *J Comput Assist Tomogr.* 1983;7:590-598.

41. Foster NL, Chase TN, Fedio P, Patronas NJ, Brooks RA, Di Chiro G. Alzheimer's disease: focal cortical changes shown by positron emission tomography. *Neurology.* 1983;33:961-965.

42. Chase TN, Foster NL, Fedio P, Brooks R, Mansi L, Di Chiro G. Regional cortical dysfunction in Alzheimer's disease as determined by positron emission tomography. *Ann Neurol.* 1984;15(suppl):170-174.

43. Duara R, Grady C, Haxby J, et al. Positron emission tomography in Alzheimer's disease. *Neurology.* 1986;36:879-887.

44. Matsui T, Hirano A. *An Atlas of the Human Brain for Computerized Tomography.* New York, NY: Igaku-Shoin Medical Publishers Inc; 1978.

45. Shimoyama M, Kito S, Itoga E, Kishida T, Nanba K. Binding experiments of muscarinic acetylcholine and dopamine receptors in human brains with emphasis on a case of striatonigral degeneration. *Jpn J Pharmacol.* 1982;32:1157-1166.

46. Enna SJ, Bennet Jr JP, Bylund DB, et al. Neurotransmitter receptor binding: regional distribution in human brain. *J Neurochem.* 1977;28:233-236.

47. Ruberg M, Ploska A, Javoy-Agid F, Agid Y. Muscarinic binding and choline acetyltransferase activity in parkinsonian subjects with reference to dementia. *Brain Res.* 1982;232:129-139.

48. Gibson RE, Weckstein DJ, Jagoda EM, Rzeszotarski WJ, Reba RC, Eckelman WC. The characteristics of I-123 r-IQNB and H-3 QNB in vivo and in vitro. *J Nucl Med.* 1984;25:214-222.

49. Gibson RE. Imaging and quantification of muscarinic acetylcholine receptors. In: Frost JJ, Wagner Jr HN, eds. *Positron Emission Tomography.* New York, NY: Raven Press. In press.

50. Johnson KA, Holman BL, Mueller SP, et al. Single photon emission computed tomography in Alzheimer's disease: abnormal iofetamine I 123 uptake reflects dementia severity. *Arch Neurol.* 1988;45:392-396.

51. Johnson KA, Mueller ST, Walshe TM, English RJ, Holman BL. Cerebral perfusion imaging in Alzheimer's disease: use of single photon emission computed tomography and iofetamine hydrochloride I 123. *Arch Neurol.* 1987;44:165-168.

52. Jagust WJ, Budinger TF, Reed BR. The diagnosis of dementia with single photon emission computed tomography. *Arch Neurol.* 1987;44:258-262.

53. Bonte FJ, Ross ED, Chehabi HH, Devous MD Sr. SPECT study of regional cerebral blood flow in Alzheimer's disease. *J Comput Assist Tomogr.* 1986;10:579-583.

54. Costa DC, Ell PJ, Burns A, Philpot M, Levy R. CBF tomograms with [^{99m}Tc]-HM-PAO in patients with dementia (Alzheimer type and HIV) and Parkinson's disease: initial results. *J Cereb Blood Flow Metab.* 1988;8(suppl):109-115.

55. Smith FW, Besson JAO, Gemmell HG, Sharp PF. The use of technetium-99m-HM-PAO in the assessment of patients with dementia and other neuropsychiatric conditions. *J Cereb Blood Flow Metab.* 1988;8(suppl):116-122.

56. Neary D, Snowden JS, Shields RA, et al. Single photon emission tomography using ^{99m}Tc-HM-PAO in the investigation of dementia. *J Neurol Neurosurg Psychiatry.* 1987;50:1101-1109.

57. Lebrun-Grandié P, Baron JC, Soussaline F, Loch'h C, Sastre J, Rousser MG. Coupling between regional blood flow and oxygen utilization in the normal human brain: a study with positron tomography and oxygen 15. *Arch Neurol.* 1983;40:230-236.

58. Herscovitch P, Raichle ME, Kilbourn MR, Welch MJ. Positron emission tomographic measurement of cerebral blood flow and permeability: surface area product of water using [^{15}O]water and [^{11}C]butanol. *J Cereb Blood Flow Metab.* 1987;7:527-542.

59. Weinberger DR, Gibson RE, Coppola R, et al. Distribution of muscarinic receptors in patients with dementia: a controlled study of ^{123}IQNB and SPECT. *J Cereb Blood Flow Metab.* 1989;9(suppl 1):537.

60. Bonner TI. The molecular basis of muscarinic receptor diversity. *Trends Neurosci.* 1989;12:148-151.

61. Birdsall NJM, Hulme EC. Biochemical studies on muscarinic acetylcholine receptors. *J Neurochem.* 1976;27:7-16.

62. Hulme EC, Birdsall NJM, Burgen ASV, Mehta P. The binding of antagonists to brain muscarinic receptors. *Mol Pharmacol.* 1978;14:737-750.

63. Zubenko GS, Moossy J, Hanin I, Martinez AJ, Rao GR, Kopp U. Bilateral symmetry of cholinergic deficits in Alzheimer's disease. *Arch Neurol.* 1988;45:255-259.

64. Sawada Y, Hiraga S, Francis B, et al. Kinetic analysis of 3-quinuclidinyl 4-[^{125}]iodobenzilate transport and specific binding to muscarinic acetylcholine receptor in rat brain in vivo: implications for human studies. *J Cereb Blood Flow Metab.* In press.

65. Di Chiro G, Brooks RA. PET quantitation: blessing and curse. *J Nucl Med.* 1988;29:1603-1604.

66. Vogt BA, Burns DL. Experimental localization of muscarinic receptor subtypes to cingulate cortical afferents and neurons. *J Neurosci.* 1988;8:643-652.

67. Mash DC, White WF, Mesulam MM. Distribution of muscarinic receptor subtypes within architectonic subregions of the primate cerebral cortex. *J Comp Neurol.* 1988;278:265-274.

68. Terry RD, Katzman R. Senile dementia of the Alzheimer type. *Ann Neurol.* 1983;14:497-506.

69. Bruno G, Mohr E, Gillespie M, Fedio P, Chase TN. Muscarinic agonist therapy of Alzheimer's disease: a clinical trial of RS-86. *Arch Neurol.* 1986;43:659-661.

70. Hansen LA, Deteress R, Tobias H, et al. Neocortical morphometry and cholinergic neurochemistry in Pick's disease. *Am J Pathol.* 1988;131:507-518.

71. Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller EA, Murphy DL. Anticholinergic sensitivity in patients with dementia of the Alzheimer type and age-matched controls: a dose-response study. *Arch Gen Psychiatry.* 1987;44:418-426.

72. Herscovitch P, Auchus AP, Gado M, Chi D, Raichle ME. Correction of positron emission tomography data for cerebral atrophy. *J Cereb Blood Flow Metab.* 1986;6:120-124.

ANTICONVULSANT BULLETIN

New evidence: No difference between the cognitive effects of phenytoin and carbamazepine

Turn page for the results of an important new study.

ANTICONVULSANT BULLETIN

Results from:
Comparative cognitive effects of anticonvulsants

K.J. Meador, D.W. Loring, K. Huh, B.B. Gallagher, D.W. King
Neurology. 1990;40:391-394.

Patients receiving phenytoin and carbamazepine had virtually identical cognitive performances[1]

- Fifteen seizure patients treated with phenytoin, carbamazepine, and phenobarbital for 3 months each were given a cognitive evaluation at the end of each treatment period[1]
- Cognitive tests were designed to assess deficits associated with anticonvulsants—impairments in memory, information processing, attention/concentration, and motor speed[1]
- Mean cognitive scores and individual responses failed to suggest a trend toward differential effects[1]

Mean scores* for cognitive measures

Cognitive Measures	Carbamazepine	Phenytoin	Phenobarbital
Grapho-Motor Coding	48	48	43
Simple Attention†	5.5	5.5	5.7
Simple Attention‡	4.0	4.5	4.5
Selective Reminding Test	53	59	49
Repetitive Motor Speed	46	45	44
Coordination/Motor Speed	72	73	74
Decisional/Motor Speed	698	705	737

—adapted from Meador et al, p 392[1]

*On Decisional/Motor Speed, it was desirable to achieve as *low* a score as possible. On all other tests, it was desirable to achieve as *high* a score as possible. However, there was no significant difference between scores of the three anticonvulsants on any test with the exception of Grapho-Motor Coding—the score for phenobarbital was significantly worse than for the other two anticonvulsants.

†Digit Span Forward. ‡Digit Span Backward.

Rigorous study design helped prevent patient selection bias—a flaw of most earlier studies

- Randomized, double-blind, triple-crossover study design helped prevent patient selection bias[1]
- Dosages were adjusted to be within the standard therapeutic range (phenytoin, 10 to 20 μg/mL; carbamazepine, 6 to 12 μg/mL; phenobarbital, 15 to 40 μg/mL)[1]

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Reference 1. Meador KJ, Loring DW, Huh K, Gallagher BB, King DW. Comparative cognitive effects of anticonvulsants. *Neurology*. 1990;40:391-394.

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Dilantin® KAPSEALS® (Extended Phenytoin Sodium Capsules, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

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Widespread Functional Effects of Discrete Thalamic Infarction

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• In order to investigate functional effects of various thalamic structures on metabolism in remote, morphologically intact cerebral regions, we used positron emission tomography of (^{18}F)-2-fluoro-2-deoxy-D-glucose to study regional cerebral metabolic rates of glucose (rCMRGlu) in 11 patients with chronic unilateral or bilateral infarcts strictly confined to the thalamus. Patients were grouped according to computed tomographic scans showing anterior (three), medial (four), or posterior (four) lesions. Compared with a matched group of 11 healthy subjects (hemispheric CMRGlu 35.2 ± 3.49 μmol/100 g per minute), glucose metabolism was significantly lower in the hemisphere ipsilateral to the infarction (31.2 ± 2.97 μmol/100 g per minute). Patients with bilateral infarcts had lower hemispheric CMRGlu (29.9 ± 2.74 μmol/100 g per minute) than those with unilateral lesions (32.2 ± 2.97 μmol/100 g per minute). Depending on infarct location within the thalamus, there was differential depression of rCMRGlu, with the largest effects on frontal and occipital areas in medial infarctions. Except for ipsilateral thalamic deactivation, metabolic patterns with anterior thalamic infarcts were close to normal, while posterior infarcts mostly depressed rCMRGlu in the visual and in the inferior limbic cortex. Cerebellar metabolic rates were within normal limits in most cases. These patterns of regional cerebral deactivation may be related to categories of thalamic projections—intrathalamic, to limbic system and basal ganglia, diffuse to most cortical areas, and specific to defined neocortical areas. Even small brain lesions may have widespread functional sequelae, potentially demonstrable by positron emission tomography.

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Functional hypometabolism in morphologically intact projection areas distant from the site of a typical cerebral infarct is a common finding in positron emission tomography (PET) of ischemic stroke.[1-6] The main cause of this transneural depression called diaschisis by von Monakow[7] was suggested to be the interruption of afferent projection systems,[8] but with chronic infarcts anterograde, wallerian degeneration may also be of functional importance.[9] Additionally, retrograde and transsynaptic degeneration secondary to the disruption of afferent pathways may play a role. The extent of remote metabolic deactivation is dependent mainly on the location of an infarct, but also the size and the severity of the ischemic damage were shown to modulate the degree of hypometabolism in areas of the central nervous system connected to the lesioned structure.[6] The thalamus being the most important relay station in the brain, modulates and coordinates almost all other cerebral functions; its projections reach nearly all areas of the telencephalon, sparing only a few.[10] From the experience with lesions in other brain structures it might be expected that rather limited destruction of the diencephalon entails metabolic depression of various distant, but functionally related, areas. However, most studies so far have investigated the effect of large subcortical lesions involving the thalamus and large fibrous projection systems, eg, in the internal capsule, and have found widespread depressions of metabolism or blood flow in the ipsilateral cortex.[11-18]

Less marked effects were also observed in the contralateral hemisphere. Regional differences of cortical depression, depending on the site of the thalamic lesion, were reported,[12] but, in contrast to animal experiments, where isolated lesions of the ventromedial thalamic nuclei caused marked decreases in metabolism of the respective cortical projection areas,[19] significant correlations could not be established in small patient series.[13] In all these previous studies, however, no clear distinction was made between discrete thalamic infarcts and those involving other subcortical structures, eg, the internal capsule, and therefore remote effects caused by thalamic nuclear destruction were not distinguished from those caused by interruption of fiber systems. It was the aim of this study to investigate the effect of chronic infarcts strictly confined to the thalamus on brain glucose metabolism in relation to thalamocortical projections.

SUBJECTS, MATERIALS, AND METHODS

Eleven patients, six females, five males, aged 39 to 67 years (mean age, 53.8 years), with unilateral or bilateral thalamic infarction, were studied. The diagnosis of ischemic stroke, which had occurred 7 months to 9 years before the PET study, was based on a typical history confirmed by a complete neurologic workup, including a computed tomographic (CT) scan obtained 1 to 5 days prior to PET. Magnetic resonance imaging scans that were available only in some cases were not consulted, in order to avoid undue chronological sample bias. Rather the CT (Somatom DR, Siemens) was used to localize the infarct and to rule out cases with involvement of structures other than the thalamus. Five infarcts were located in the left thalamus, one in the right thalamus, and five patients had bilateral thalamic infarction. Three infarcts involved mainly the anterior, four mainly the medial, and four the (ventrolateral) posterior thalamic regions. Three of the medial and one each of the posterior and anterior infarcts were bilateral. Clinical assessment of these patients with chronic thalamic infarction (Table 1) revealed dementia with prominent amnesia in seven cases; three patients presented with aphasic syndromes, with anomia in two and articulatory initiation problems in one case. Three patients suffered from (incomplete) Déjerine-Roussy syndrome with thalamic pain. In none of our cases, loss of motor or sensory function indicated a lesion of internal capsule or midbrain structures, thus providing further evidence to the fact that only patients with infarcts restricted to the thalamus were studied.

After written informed consent had been obtained from the patient whenever possible, and/or from his next of kin, brain glucose metabolism (CMRGlu) was studied with 2(^{18}F)-fluoro-2-deoxy-D-glucose (FDG) and PET,[20] using a four-ring positron camera (Scanditronix PC-384) simultaneously scanning seven slices (11 mm in thickness)

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Table 1.—Clinical Data of Patients With Pure Thalamic Infarct

Patient No./ Sex/Age, y	No. of Years After Infarction	Thalamic Lesion	Clinical Syndrome
MH/F/43	0.6	anterior left, right	Amnesia, aphasia (anomia)
AU/F/57	2.5	anterior left	Amnesia
FZ/F/45	2.8	anterior left	Dementia with prominent amnesia
ME/F/39	0.9	medial right, left	Dementia with prominent amnesia, aphasia (anomia), dysarthria
LE/M/67	1.1	medial left, right	Dementia with prominent amnesia
HO/M/46	5.0	medial right, left	Amnesia
MD/F/62	5.0	medial left	Aphasia (articulatory initiation deficit and anomia)
ML/F/61	9.0	posterior right	Incomplete Déjerine-Roussy syndrome, dementia
KG/M/54	4.5	posterior left	Déjerine-Roussy syndrome, dementia
WJ/M/64	6.0	posterior left	Déjerine-Roussy syndrome, dementia
MF/M/54	4.0	posterior right, left	Dementia, prominent amnesia

Table 2.—Regional Cerebral Metabolic Rate of Glucose in Affected Hemisphere*

Region	Control (n = 11)	All Infarcts (n = 11)	Anterior Infarcts (n = 3)	Medial Infarcts (n = 4)	Posterior Infarcts (n = 4)
Hemispheric average	35.2 ± 3.49	31.2 ± 2.97	34.1 ± 3.66	29.3 ± 1.95	30.9 ± 1.89
Frontal cortex	40.5 ± 4.25	35.2 ± 3.80	38.6 ± 4.82	32.0 ± 2.22	35.8 ± 1.57
Lateral temporal cortex	35.7 ± 3.30	33.2 ± 3.06	35.9 ± 3.45	31.2 ± 2.16	33.0 ± 2.44
Insular cortex	39.6 ± 4.81	33.8 ± 4.31	38.0 ± 5.49	31.8 ± 2.96	32.7 ± 2.94
Sensorimotor cortex	39.9 ± 4.35	35.3 ± 3.49	38.9 ± 4.21	33.3 ± 2.36	34.5 ± 2.13
Parietal cortex	37.6 ± 3.98	34.1 ± 3.65	37.3 ± 4.06	32.7 ± 3.63	33.0 ± 2.41
Occipital convex cortex	37.9 ± 3.48	35.3 ± 3.50	39.0 ± 3.85	33.0 ± 1.69	34.8 ± 2.71
Primary visual cortex	39.8 ± 7.82	35.2 ± 3.52	37.6 ± 3.42	35.9 ± 2.17	32.7 ± 3.71
Mesial temporal cortex	29.6 ± 3.37	27.6 ± 2.67	28.8 ± 1.86	28.5 ± 0.88	25.7 ± 3.62
Cingulate cortex	43.6 ± 4.61	38.1 ± 4.67	43.1 ± 4.33	35.2 ± 3.49	37.4 ± 3.40
Caudate nucleus	42.0 ± 5.70	36.9 ± 4.13	40.7 ± 4.93	35.6 ± 4.36	35.4 ± 1.42
Lentiform nucleus	43.1 ± 6.76	38.4 ± 5.73	43.4 ± 8.09	34.5 ± 3.68	38.6 ± 2.62
Thalamus†	39.9 ± 7.28	29.3 ± 2.89	31.2 ± 2.14	28.9 ± 3.39	28.3 ± 2.84
Cerebellum (contralateral)	32.7 ± 3.53	29.7 ± 3.10	31.2 ± 2.17	30.9 ± 2.04	27.5 ± 3.74

*Values for regional cerebral metabolic rate of glucose are given in micromoles per 100 g per minute. Values are means ± SDs.

†Noninfarcted tissue only.

at an in-slice spatial resolution of 7.8 mm full width at half maximum height (FWHM).[21] After patient positioning by means of laser beams and skin marks, 185 MBq (5 mCi) FDG synthesized according to the method of Ehrenkaufer et al[22] was injected intravenously, with the patient resting in a darkened room with low ambient noise, eyes closed, and ears unoccluded. The first set of seven tomograms was recorded from 30 to 40 minutes after injection, the patients were then axially shifted by 7 mm to permit the scanning of an additional set of seven intercalated slices. Investigative and scanning procedures, as well as image processing, were performed as described in detail elsewhere.[23] The CMRGlu in the 14 parallel slices scanned between 30 and 50 minutes after FDG injection was calculated using a lumped constant of 0.42 and rate constants adjusted for the measured tissue activities according to a K_1-k_3 optimization procedure[24] requiring less stringent assumptions about the tracer behavior in abnormal tissue. Standardized regional quantitation was achieved by means of an interactive mapping program[25] and a categorical region-matching and block-shifting procedure[26] providing optimal comparability among subjects. The effect of anterior, medial, or posterior thalamic infarction on CMRGlu was studied in 14 cluster brain regions usually comprising several slices: brain stem, cerebellum, white matter, unaffected thalamus, caudate and lentiform nucleus, and frontal, lateral temporal, mesiotemporal, insular, parietal, sensorimotor, visual, and cingulate cortex. These data were compared with the results obtained in 11 healthy subjects matched for age and sex. No attempt was made to establish a control group with mild systemic or cardiovascular health problems, because such risk factors apparently have no significant effect on brain metabolism,[27] while patients with extrathalamic stroke do not lend themselves for comparison, considering their prominent deactivation pattern.[6]

Hemispheric CMRGlu was calculated as the average of all regional CMRGlu values weighted by region size. In normal subjects and patients with bilateral infarcts, averages of both hemispheres and of corresponding regions within both hemispheres were calculated and used for further analysis, whereas in patients with unilateral infarcts ipsilateral and contralateral hemispheres were treated separately. Data were analyzed by analysis of variance (ANOVA), with the regions representing the levels of a within-subject factor, using the Huynh and Feldt[28] correction of degrees of freedom. Values are given as means ± SDs.

RESULTS

Effects of Thalamic Infarction on Hemispheric Metabolic Rate

The mean (ipsilateral) hemispheric and regional CMRGlu of the 11 patients with thalamic infarction, and of the volunteer subjects, are summarized in Table 2. In a comparison of control subjects vs patients (hemispheres ipsilateral to infarct only), hemispheric CMRGlu was significantly lower in patients ($P = .009$). Comparing patients with bilateral infarcts vs ipsilateral and contralateral hemispheres of patients with unilateral infarcts and normal subjects, hemispheric CMRGlu was most severely depressed in patients with bilateral thalamic lesions (29.9 ± 2.74 μmol/100 g per minute, $P = .05$ in Tukey's multiple-range test), while unilateral infarcts decreased CMRGlu in the ipsilateral hemisphere only to 32.2 ± 2.97 μmol/100 g per minute and had little effect on CMRGlu of the contralateral hemisphere (34.1 ± 3.85 μmol/100 g per minute) (Fig 1).

Effects on Regional Metabolic Rates

The dependence on infarct location of the ipsilateral pattern of metabolic depression was analyzed by ANOVA of regional differences from hemispheric mean values. There was a significant interaction between infarct location and regional metabolism ($P = .035$). Post hoc contrasts of individual regions demonstrated that the effect was most pronounced in frontal and occipital areas ($P = .007$ and $P = .054$, respectively), where medial thalamic infarcts caused the largest metabolic depression.

For detailed analysis, the profile deviation from normal control subjects of regional cortical values was plotted (Fig 2). The profile of anterior infarcts was close to normal (Fig 3). Frontal hypometabolism was most pronounced in medial infarcts (Fig 4), whereas CMRGlu in visual and mesiotemporal cortex was most severely affected in posterior thalamic infarcts (Fig 5).

In a separate analysis of subcortical

structures, noninfarcted homolateral thalamic tissue was found severely deactivated ($P = .001$), but CMRGlu in contralateral thalamus was not significantly affected. Especially in patients with larger thalamic lesions, while these values may suffer from partial volume effects not permitting a clear separation of infarcted and noninfarcted tissue, a marked decrease of thalamic CMRGlu was also observed in patients with small lesions (eg, small anterior infarct, as shown in Fig 3), which did not cause a striking effect on most cortical areas.

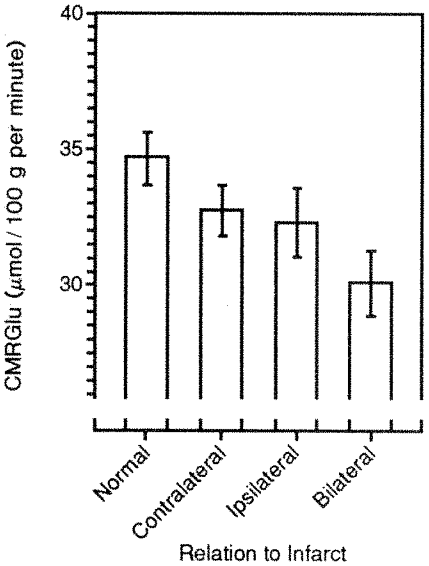


Fig 1.—Mean regional cerebral metabolic rates of glucose (CMRGlu) in hemispheres of normal volunteers (n = 11, mean of both hemispheres), in hemispheres contralateral and ipsilateral to unilateral thalamic infarcts (n = 6), and in hemispheres of patients with bilateral thalamic infarcts (n = 5, mean of both hemispheres). Error bars indicate SEM.

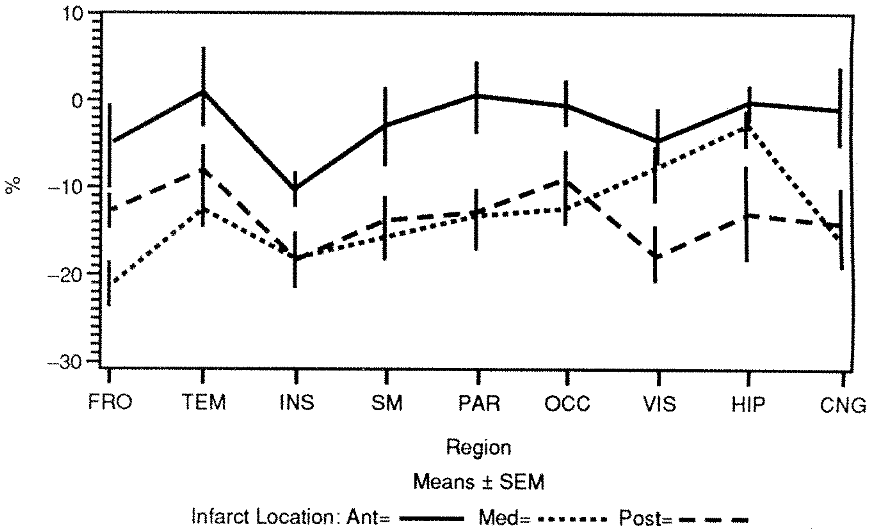


Fig 2.—Difference from normal control subjects of regional cortical cerebral metabolic rates of glucose (CMRGlu) in affected hemispheres of patients with thalamic infarcts grouped according to location of lesion. Anterior (ANT) thalamic infarcts induced little deviation from normal CMRGlu pattern; with medial (MED) infarcts, metabolic decreases were most pronounced in frontal cortex; posterior (POST) lesions had largest effect on visual cortex and hippocampal structures. FRO indicates frontal cortex; TEM, lateral temporal cortex; INS, insular cortex; SM sensorimotor cortex; PAR, parietal cortex; OCC, occipital convexity cortex; VIS, primary visual cortex; HIP, mesial temporal cortex; and CNG, cingulate cortex.

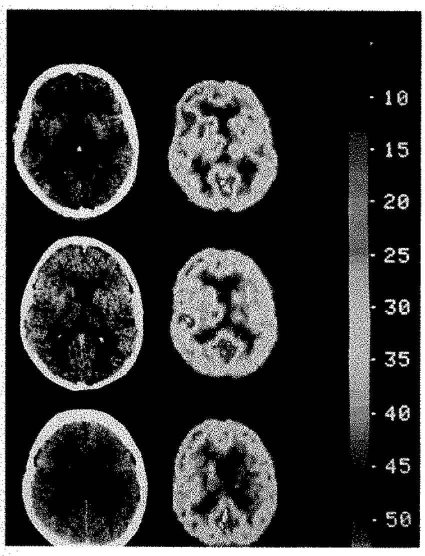


Fig 3.—Computed tomographic and (^{18}F)-2-fluoro-2-deoxy-D-glucose-positron emission tomographic images at three levels (centered around middle part of thalamus) in patient 1 with unilateral infarct in left anterior thalamus. Thalamic lesion has low glucose metabolism, but also noninfarcted thalamus is metabolically depressed. Other regional cerebral metabolic rates of glucose values are in normal range. Gray scale indicates cerebral metabolic rates of glucose values in micromoles per 100 g per minute.

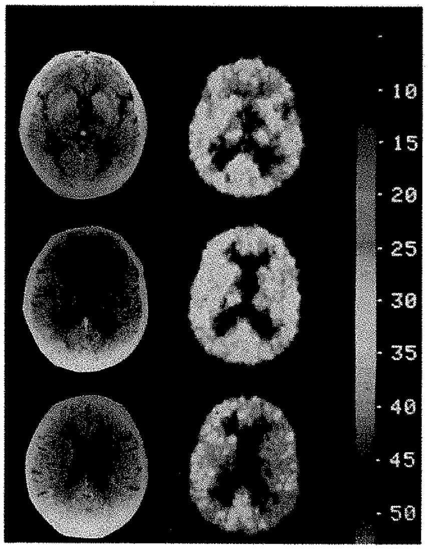


Fig 4.—Computed tomographic and (^{18}F)-2-fluoro-2-deoxy-D-glucose-positron emission tomographic images at three levels (centered around middle part of thalamus) in patient 5 with bilateral infarcts in medial thalamus. Glucose metabolism is diffusely decreased with most pronounced effects on frontal cortex. Gray scale indicates cerebral metabolic rates of glucose in micromoles per 100 g per minute.

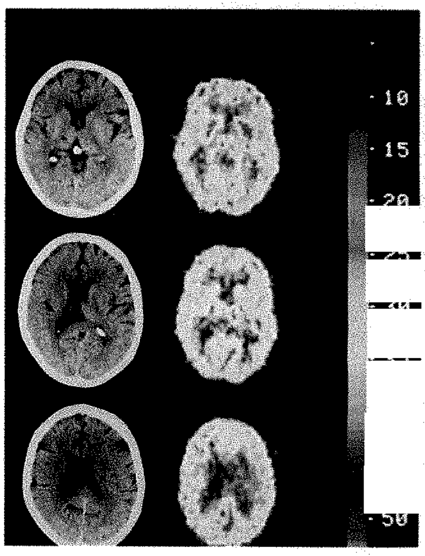


Fig 5.—Computed tomographic and (^{18}F)-2-fluoro-2-deoxy-D-glucose-positron emission tomographic images at three levels (centered around middle part of thalamus) in patient 8 with unilateral infarct in right posterior thalamus (posterolateral ventral nucleus). Regional depression of cerebral metabolic rate of glucose in occipital cortex. Gray scale indicates cerebral metabolic rates of glucose in micromoles per 100 g per minute.

Regional CMRGlu of the basal ganglia was mainly affected by lesions in the medial thalamus, while the values measured in the anterior and posterior group were only slightly below those found in the control subjects. Metabolic rates of glucose in the cerebellum were within the normal range in all but one case with a bilateral posterior infarct. Group differences were not significant.

COMMENT

The thalamus, being the most important subcortical relay center for exteroceptive and proprioceptive stimuli, plays a fundamental role in the integration and coordination of information going to the cortex, but it is also an essential part of the ascending reticular and limbic systems, and it has important connections with the basal ganglia and receives input from the cerebellum.[10] The main efferent pathways can be grouped into the following four categories[29]: (1) fibers to circumscribed and well-defined areas of the neocortex from specific relay nuclei with strict somatotropic projections; (2) fibers to the limbic system and the basal ganglia; (3) fibers projecting diffusely into most cortical areas; and (4) intrathalamic connecting fibers not leaving the thalamus.

Based on the concept of functional deactivation or activation as a metabolic indicator of impaired input to identifiable brain structures, PET can be used to follow projection systems when the nuclei where efferent fibers originate are selectively destroyed or stimulated.

This concept was successfully applied to the study of metabolic activation during simple or complex physiologic stimulation and during the performance of various tasks, thereby opening a new venue for functional neuroanatomy in the intact individual.[30-32] This approach can also be used to demonstrate the metabolic depression in areas connected to lesioned brain structures. Therefore, it may help—like degeneration studies in classical neuroanatomy—in the identification of the target region of projection systems and in the interpretation of complex clinical syndromes caused by focal tissue damage. Considering the limited spatial resolution of PET, effects on small structures, eg, the individual thalamic nuclei, where intrathalamic fibers project to can hardly be visualized, thus limiting the application of this method to large thalamic projection fields outside the thalamus. Despite these limitations, our study indicated that noninfarcted thalamic structures have decreased metabolism consequent to the lack of intrathalamic input.

Most studies so far have shown global reductions of metabolism and blood flow as a result of thalamic infarction,[12,13,16,18] while regional effects did not reach statistical significance. This conclusion, which can also be derived from a first look at our data (Table 2), emphasizes effects mediated by the diffuse projection of various thalamic nuclei—mainly the centromedian and intralaminar nuclei—to widespread cortical and subcortical areas. Therefore, the global metabolic depression was most marked in the group with medial thalamic infarctions that always involved major intralaminar nuclei. However, more detailed statistical analysis of our data suggests another interpretation that also fits to the accepted function of thalamic relay nuclei: the metabolic rate of various brain regions obviously is selectively affected by thalamic infarctions, and this selectivity depends on the location of the infarction within the thalamus. The sum of these regional effects, together with a global depression, would then cause metabolic decreases observed in the whole hemisphere. The areas of significant metabolic depression in the three infarct location groups corresponded with the main anatomical projections: The marked metabolic deactivation (20% decrease of rCMRGlu, compared with control subjects) in the frontal lobe of patients with medial thalamic infarction corresponds with the large projections of the medial thalamic nucleus to this region, while the widespread additional cortical effects are probably due to the diffuse projections originating in centromedian and other intralaminar nuclei involved in infarctions in the medial portion of the thalamus. In contrast, regional effects of posterior infarcts were most prominent in the visual, parietal, insular, and sensorimotor areas. These effects may be ascribed to the specific projections from lateral, posterior, and ventroposterior nuclei. The apparent similarity of regional effects of medial and posterior infarctions may be explained either by some involvement of diffusely projecting nuclei, or by the unprecise separation of infarct locations on CT. In contrast, anterior thalamic infarctions caused no significant regional metabolic depression despite large projections from the anterior nucleus to the cingulate gyrus. While such an effect might have escaped detection in this small group due to the limited spatial resolution, a decrease of CMRGlu in nonaffected thalamic nuclei was obvious and may have produced the clinical symptoms, eg, the memory and cognitive disturbances prominent in these cases.

Our results are also in good agreement with the hypothesis of some major involvement of efferent thalamic fibers projecting to subcortical and limbic structures: medial infarctions depress metabolism in the lentiform and caudate nuclei, since a main tract leads from the centromedian nucleus to the putamen, while more ventromedial intralaminar nuclei affect the metabolic rate in the caudate nucleus.[33] From various parts of the thalamus sizable projections lead to limbic structures (anterior nucleus-cingulate gyrus, medial nucleus-amygdaloid body, dorsolateral nucleus-hippocampus and cingulate gyrus). However, the metabolic effects on limbic structures observed in our small groups (more marked effect on cingulate gyrus with medial, and on mesial temporal and cingulate structures with posterior lesions) did not fully correspond with these connections. Obviously, the involvement of the limbic system and the deactivation of reticular nuclei additionally influences global brain metabolism by indirect mechanisms.

In two cases studied with PET during stimulation by electrodes implanted into the ventral posterior nucleus for pain treatment, global metabolism was decreased by 20% in both hemispheres, while the pattern of specific metabolic regional effects was similar to the unstimulated state.[12] This finding, which contrasts with the enhancement during stimulation observed by Katayama et al,[34] may be interpreted as corresponding with decreased anxiety due to pain relief. However, fibers diffusely projecting from thalamic nuclei to the cortex and synapsing in layer four on inhibitory Golgi II cells (stellate cells) were described,[29,35] which may mediate a widespread deactivation.

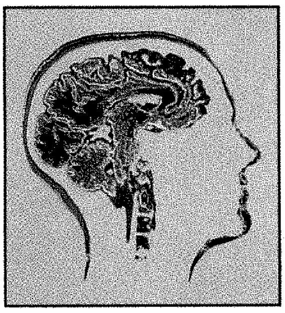
In previous investigations, some of the significant regional effects established in our group of selected patients with isolated thalamic infarctions were reported in an anecdotal way: two of the patients described by Baron et al[13] had infarcts restricted to anterior and medial nuclei, and distinct functional depression was found in frontal parietal cortex; two with posterior lesions showed temporo-occipital hypometabolism. In five of the 10 cases presented by Baron et al,[13] the infarction widely exceeded the thalamus, and this was also the case in most patients included in the other studies.[12,16,18] These mixed cohorts of patients, who, in contrast with the cases selected for this study, also presented motor or sensory deficits clearly not due to thalamic lesions, hampered the interpretation of results and weakened their statistical analysis. The finding of occasional contralateral cerebellar deactivation[12,18] may be statistically significant only in samples of larger size, or it may be related to a lesion of the internal capsule, since the thalamus has afferent but no direct efferent connections with the cerebellum. The 11 patients in our study were carefully selected to have infarctions restricted to the thalamus on CT. These patients suffered from symptoms caused exclusively by thalamic lesions, ie, dementia with prominent amnestic syndromes, Déjerine-Roussy syndrome, and language problems. In none of the patients were symptoms related to lesions in other locations present, which were reported to be part of the clinical syndrome in the other studies.[13,18]

Our study has various limitations as to the functional assessment of thalamic projections. The number of cases was small, preventing further subgrouping. The identification of individual nuclei involved in the infarct could not be achieved by CT, and magnetic resonance imaging scans were not consistently available. Therefore, only three categories—anterior, medial, and posterior infarcts—were used with some overlap in the involvement of ventral and lateral nuclei. The limited spatial resolution of PET did not permit the quantification of metabolic rates in very small brain structures and, together with the poor identification of affected nuclei on CT, prevented a clear somatotropic (point-to-point) correspondence between thalamic lesion and metabolically inactivated structures. Nevertheless, this study emphasizes the potential of PET for analyzing the effect of small lesions in the thalamus on the function of remote brain regions: For all four categories of thalamic projections,[29] typical depression of glucose metabolism due to specific thalamic lesions was evident. Therefore, our results encourage further investigations, with improved technology on larger groups of patients, to shed more light on the intricate functional anatomy of the thalamus. Especially in cases with thalamic infarction, where the extent of the lesion is not restricted to individual nuclei or groups of nuclei but is due to the complex and variable supply from the internal carotid, posterior communicating, and posterior cerebral arteries,[36] PET studies of the pattern of metabolic deactivation can afford more insight into the primarily affected structures and thereby improve diagnostic classification.

References

1. Kuhl DE, Phelps ME, Howell AP, et al. Effects of stroke on local cerebral metabolism and perfusion: mapping by emission computed tomography of 18FDG and 13NH3. *Ann Neurol.* 1980;8:47-60.
2. Baron JC, Bousser MG, Comar D, et al. 'Crossed cerebellar diaschis' in human supratentorial brain infarction. *Trans Am Neurol Assoc.* 1980;105:459-461.
3. Heiss WD, Ilsen HW, Wagner R, et al. Remote functional depression of glucose metabolism in stroke and its alteration by activating drugs. In: Heiss WD, Phelps ME, eds. *Positron Emission Tomography of the Brain.* Berlin, Federal Republic of Germany: Springer Verlag; 1983:162-168.
4. Martin WRW, Raichle ME. Cerebellar blood flow and metabolism in cerebral hemisphere infarction. *Ann Neurol.* 1983;14:168-176.
5. Kushner M, Alavi A, Reivich M, et al. Contralateral cerebellar hypometabolism following cerebral insult: a positron emission tomographic study. *Ann Neurol.* 1984;15:425-434.
6. Pawlik G, Herholz K, Beil C, et al. Remote effects of focal lesions on cerebral flow and metabolism. In: Heiss WD, ed. *Functional Mapping of the Brain in Vascular Disorders.* Berlin, Federal Republic of Germany: Springer Verlag; 1985:59-83.
7. von Monakow C. *Die Lokalisation im Grosshirn und der Abbau der Funktion durch kortikale Herde.* Wiesbaden, Federal Republic of Germany: Bergmann; 1914.
8. Powers WJ, Raichle ME. Positron emission tomography and its application to the study of cerebrovascular disease in man. *Stroke.* 1985;16:361-376.
9. Duchen LW. General pathology of neurons and neuroglia. In: Adams JH, Corsellis JAN, Duchen LW, eds. *Greenfield's Neuropathology.* London, England: E Arnold; 1984:1-52.
10. Leonhardt H, Krisch B, Zilles K. Graue und weiße Substanz des Zwischenhirns. In: Leonhardt H, Tillmann B, Töndury G, Zilles K, eds. *Anatomie des Menschen.* Stuttgart, Federal Republic of Germany: Georg Thieme; 1987;3:319-369.
11. Metter EJ, Riege WH, Hanson WR, et al. Comparisons of metabolic rates, language and memory in subcortical aphasias. *Brain Lang.* 1983;19:33-47.
12. Pawlik G, Beil C, Herholz K, et al. Comparative dynamic FDG-PET study of functional deactivation in thalamic versus extrathalamic focal ischemic brain lesions. *J Cereb Blood Flow Metab.* 1985;5(suppl 1):S9-S10.
13. Baron JC, D'Antona R, Pantano P, et al. Effects of thalamic stroke on energy metabolism of the cerebral cortex. *Brain.* 1986;109:1243-1259.
14. Rosseaux M, Steinling M, Petit H, et al. Perturbations du débit sanguin hémisphérique et hématomes cérébraux profonds. *Rev Neurol (Paris).* 1986;4:480-488.
15. Perani D, Vallar G, Cappa S, et al. Aphasia and neglect after subcortical stroke. *Brain.* 1987;110:1211-1229.
16. Cambon H, Baron JC, Pappata S, et al. Recovery of cortical metabolism after thalamic lesions in humans: a manifestation of plasticity? *J Cereb Blood Flow Metab.* 1987;7(suppl 1):S194.
17. Olsen TS, Bruhn P, Öberg RGE. Cortical hypoperfusion as a possible cause of subcortical aphasia. *Brain.* 1986;109:393-410.
18. Pappata S, Cambon H, Samson Y, et al. Remote metabolic effects of thalamic and capsular stroke: clinical-topographical correlations. *J Cereb Blood Flow Metab.* 1987;7(suppl 1):S42.
19. Girault JA, Savaki HE, Desban M, et al. Bilateral cerebral metabolic alterations following lesion of the ventromedial thalamic nucleus: mapping by the ^{14}C-deoxyglucose method in conscious rats. *J Compar Neurol.* 1985;231:137-149.
20. Reivich M, Kuhl D, Wolf A, et al. The (^{18}F)-fluorodeoxyglucose method for the measurement of local cerebral glucose utilization in man. *Circ Res.* 1979;44:127-137.
21. Eriksson L, Bohm C, Kesselberg M, et al. A four ring positron camera system for emission tomography of the brain. *IEEE Trans Nucl Sci.* 1982;29:539-543.
22. Ehrenkaufer RE, Potocki JE, Jewett DM. Simple synthesis of ^{18}F-labeled 2-fluoro-2-deoxy-D-glucose: concise communication. *J Nucl Med.* 1984;25:333-337.
23. Heiss WD, Pawlik G, Herholz K, et al. Regional kinetic constants and CMRGlu in normal human volunteers determined by dynamic positron emission tomography of (^{18}F)-2-fluoro-2-deoxy-D-glucose. *J Cereb Blood Flow Metab.* 1984;4:212-223.
24. Wienhard K, Pawlik G, Herholz K, et al. Estimation of local cerebral glucose utilization by positron emission tomography of (^{18}F)-2-fluoro-2-deoxy-D-glucose: a critical appraisal of optimization procedures. *J Cereb Blood Flow Metab.* 1985;5:115-125.
25. Herholz K, Pawlik G, Wienhard K, et al. Computer assisted mapping in quantitative analysis of cerebral positron emission tomograms. *J Comput Assist Tomogr.* 1985;9:154-161.
26. Pawlik G, Herholz K, Wienhard K, et al. Some maximum likelihood methods useful for the regional analysis of dynamic PET data on brain glucose metabolism. In: Bacharach SL, ed. *Information Processing in Medical Imaging.* Dordrecht, the Netherlands: M Nijhoff Publisher; 1986:298-310.
27. Chawluk JB, Alavi A, Jamieson DG, et al. Changes in local cerebral glucose metabolism with normal aging: the effects of cardiovascular and systemic health factors. *J Cereb Blood Flow Metab.* 1987;7(suppl 1):S411.
28. Huynh H, Feldt LS. Estimation of the Box correction for degrees of freedom from sample data in the randomized block and split plot designs. *J Educ Stat.* 1976;1:69-82.
29. Creutzfeldt OD: *Cortex Cerebri.* Berlin, Federal Republic of Germany: Springer Verlag; 1983.
30. Phelps ME, Mazziotta JC, Huang SC. Study of cerebral function with positron computed tomography. *J Cereb Blood Flow Metab.* 1982;2:113-162.
31. Raichle ME. Circulatory and metabolic correlates of brain function in normal humans. In: Plum F, ed. *Handbook of Physiology.* Bethesda, Md: American Physiological Society; 1987;1:643-674.
32. Pawlik G, Heiss WD. Positron emission tomography and neuropsychological function. In: Bigler ED, Yeo RA, Turkheimer E, eds. *Neuropsychological Function and Brain Imaging.* New York, NY: Plenum Publishing Corp; 1989:65-138.
33. Mehler WR. Further notes on the centre median, nucleus of Luys. In: Purpura DP, Yahr MD, eds. *The Thalamus.* New York, NY: Columbia University Press; 1966:109-127.
34. Katayama Y, Tsubokawa T, Hirayama T, et al. Response of regional cerebral blood flow and oxygen metabolism to thalamic stimulation in humans as revealed by positron emission tomography. *J Cereb Blood Flow Metab.* 1986;6:637-641.
35. White EL. Identified neurons in mouse SmI cortex which are postsynaptic to thalamo-cortical axon terminals: a combined Golgi-electron microscopic and degeneration study. *J Comp Neurol.* 1978;181:627-662.
36. Foix CH, Hillemand P. Les artères de l'axe encéphalique jusqu'au diencéphale inclusivement. *Rev Neurol.* 1925;44:705-739.

THROUGH A CALCIUM-MODULATING MECHANISM OF ACTION



CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

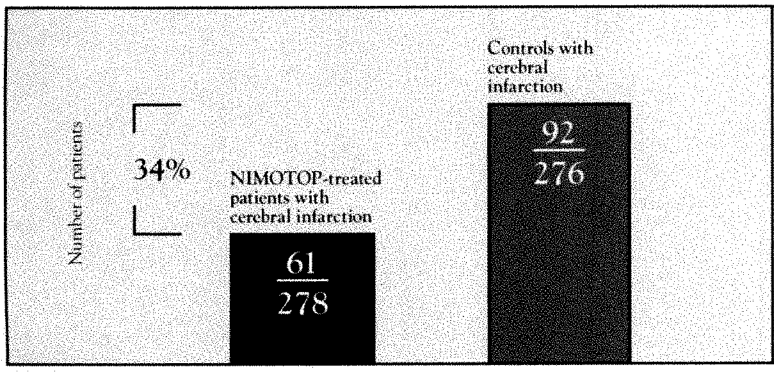
CAPSULES 30 mg

REDUCES INCIDENCE OF CEREBRAL INFARCTION IN PATIENTS FOLLOWING SUBARACHNOID HEMORRHAGE

In the largest study to date, NIMOTOP demonstrated a significant reduction in incidence of cerebral infarction[1]

- Twenty-two percent (61/278) of NIMOTOP-treated patients experienced cerebral infarction vs. 33% (92/276) of controls
- NIMOTOP reduced the incidence of cerebral infarction by 34%

Thirty-four percent reduction in incidence of cerebral infarction with NIMOTOP-treated patients vs. controls (n=554; p=0.003)[1]*



*90% of patients in this study were Hunt and Hess Grades I-III.

Dose: 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 days commencing within 96 hours of SAH.

Adapted from Pickard, et al.[1]

NIMOTOP modulates calcium influx to promote cerebral perfusion, and may directly protect neurons[2-5]

"[In animals] The beneficial cytoprotective effect of nimodipine, probably related to normalization of calcium homeostasis and blood-brain barrier permeability after ischemia, may reflect both vascular and cellular sites of action."[6]

Lazarewicz JW, et al. *Stroke* 1989.

"[In humans] The data thus suggest that nimodipine neither prevents nor reverses cerebral vasospasm. Calcium channel blockers such as nimodipine may have an effect on cerebral arterioles that are below the limits of resolution of angiography. . . . "[1]

Pickard JD, et al. *Br Med J* 1989.

MILES

Please see references and Brief Summary of full prescribing information on next page.

CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

NIMOTOP REDUCES THE INCIDENCE OF CEREBRAL INFARCTION FOLLOWING SUBARACHNOID HEMORRHAGE

BRIEF SUMMARY
NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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REFERENCES
1. Pickard JD, Murray GD, Illingworth R, et al. *Br Med J.* 1989;298:636-642. 2. Solomon RA, Fink ME. *Arch Neurol.* 1987;44:769-773. 3. Petruk KC, West M, Mohr G, et al. *J Neurosurg.* 1988;68:505-517. 4. Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. *Acta Neurol Scand.* 1987;76:267-271. 5. Scriabine A, van den Kerckhoff W. *Ann NY Acad Sci.* 1988;522:698-706. 6. Lazarewicz JW, Pluta R, Salinska E, Puka M. *Stroke.* 1989;20:70-77.

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Spectral Analysis of Heart Rate in Diabetic Autonomic Neuropathy

A Comparison With Standard Tests of Autonomic Function

Roy Freeman, MD; J. Philip Saul, MD; Mark S. Roberts, MD, MPP; Ronald D. Berger, MD, PhD;
Christopher Broadbridge; Richard J. Cohen, MD, PhD

• Power spectral analysis of the heart rate was compared with standard tests of autonomic function performed on 15 insulin-dependent diabetic patients with symptoms of autonomic dysfunction. The high-frequency power, low-frequency power, and total power of the heart rate power spectrum measured in the supine position—possible measures of parasympathetic nervous system function—were significant predictors of the expiratory-inspiratory ratio, the beat-to-beat heart rate difference on deep respiration, the standard deviation of the resting heart rate, the 30:15 ratio, and the Valsalva ratio. The change in low-frequency power on moving from the supine to upright position, a possible measure of sympathetic nervous system function, was a modest predictor of the systolic and diastolic blood pressure fall in response to postural change, but a poor predictor of the blood pressure response to isometric exercise and a cold stimulus. This study supports the role of heart rate power spectral analysis as a clinical test of autonomic function in patients with known or suspected autonomic failure.

(*Arch Neurol.* 1991;48:185-190)

Autonomic neuropathy is a frequent complication of diabetes and has a wide range of clinical presentations.[1] Although there is no gold-standard measure of autonomic dysfunction, over the past 15 years, several tests assessing cardiovascular autonomic function have been described. These include measures of heart rate variation, baroreceptor function, and cardiovascular responsivity to postural change, cold pressor, and exercise.[2] These tests have been criticized as being insensitive to early changes in autonomic function, particularly sympathetic nervous system dysfunction.[3] They also require active patient participation, which is difficult to standardize. Power spectral analysis of the resting heart rate has recently been introduced as a test of autonomic function. This technique may answer these criticisms and may provide an accurate, sensitive, and specific single test of autonomic function, measuring both parasympathetic and sympathetic divisions of the autonomic nervous system and requiring minimal patient cooperation. Prior to the widespread introduction of power spectral analysis as a measure of autonomic function, it is important to compare this technique with the standard tests of autonomic function.

Spectral analysis reduces a signal to the sum of its component sine waves of different amplitudes and frequencies. The power spectrum displays the squared amplitude of these sine waves as a function of frequency, thus expressing the variance as a function of frequency. Heart rate fluctuations, which reflect modulation of sinus node activity by autonomic and other homeostatic mechanisms, can be quantified and displayed using this technique. Power spectral analysis may thus provide a useful noninvasive technique for analyzing the autonomic mechanisms that control heart rate.[4]

Spectral analysis of the resting heart rate commonly produces several prominent peaks (Fig 1). The peak found at the highest frequency (greater than 0.15 Hz) reflects oscillations of heart rate that occur with respiration—the respiratory sinus arrhythmia.[4,5] Quantification of these oscillations provides a measure of the response of the sinus node to fluctuations in vagal nerve activity at the respiratory frequency and is reduced by parasympathetic pharmacological blockade.[5] Oscillations in heart rate at frequencies less than 0.15 Hz are mediated by both the vagus and the cardiac sympathetic nerves. Spectral power within the 0.05- to 0.15-Hz frequency band most likely represents baroreceptor feedback activity, while the spectral power at less than 0.05 Hz may reflect both cardiac autonomic input as well as the influence of circulating catecholamines.[6,7] In normal subjects, the move from the supine to upright position produces a shift in the power spectrum from high to low frequencies (Fig 1). This shift in spectral power, induced by a postural change, is reduced by β-adrenergic receptor blockade and may provide an index of sympathetic activity.[5]

In this study, we performed spectral analysis of the heart rate and standard tests of autonomic function on 15 insulin-dependent diabetic patients with symptoms of autonomic dysfunction, in order to compare indexes derived from the heart rate-power spectrum with the range of values occurring with standard tests performed on patients with suspected autonomic dys-

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function. To our knowledge, no study to date has compared spectral analysis with individual tests of autonomic function.

PATIENTS AND METHODS

Fifteen insulin-dependent diabetic patients with symptoms of autonomic dysfunction had standard tests of autonomic function and spectral analysis of the heart rate performed. The mean age was 41.1 ± 20.0 years, with a mean duration of diabetes of 10.9 ± 8.7 years. All testing was carried out in the Autonomic Evaluation Unit of the New England Deaconess Hospital, Boston, Mass. Blood pressure was measured with a noninvasive vital sign monitor (Critikon Dinamap 1846SX/P, Tampa, Fla) connected to an IBM personal computer AT via an RS232 serial interface board. Heart rate for standard tests of autonomic function was measured by an electrocardiographic monitor (Hewlett-Packard, model 78203A, Waltham, Mass), connected to the microcomputer via a data acquisition board (MetraByte Dash-8). The time interval between two successive R waves detected by the electrocardiographic monitor was translated to heart rate and recorded by the microcomputer in real time.

Patients were given sufficient time to attain baseline autonomic function. Basal state measurements (systolic blood pressure, diastolic blood pressure, mean arterial blood pressure, and heart rate) were obtained in the supine position.

Standard Autonomic Test Methods

Heart Rate Variation at Rest.—The SD of 150 consecutive R-R intervals, recorded while the subject lay quietly breathing, was calculated.[8,9]

Heart Rate Variation With Respiration.—Patients were trained to breathe at the rate of six breaths per minute in the sitting position. The ratio of the six longest to the six shortest R-R intervals was determined (expiratory-inspiratory [E-I] ratio).[10] The difference between the maximum and minimum heart rates (Max − Min) was calculated.[11]

The Valsalva Maneuver.—The seated patient was asked to expire for 15 to 20 seconds against a resistance of 40 mm Hg in an open loop system. The Valsalva ratio, the ratio of the maximum heart rate during the expiratory phase to the minimum heart rate during the relaxation phase, was calculated.[12]

The Cold Pressor Test.—The increase in systolic blood pressure after the patient placed his/her hand in cold water (4°C) for 60 seconds was determined.[13]

Isometric Exercise.—The patient was instructed to squeeze a handgrip dynamometer at 30% of his maximal effort for 4 minutes. Careful attention was paid to ensure adequate effort by all patients. The increase in diastolic blood pressure was determined.[14]

The Hemodynamic Response to Tilt Table Testing.—The blood pressure and heart rate were measured over 5 minutes following passive tilting to 60°. The change in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure, was recorded.[15]

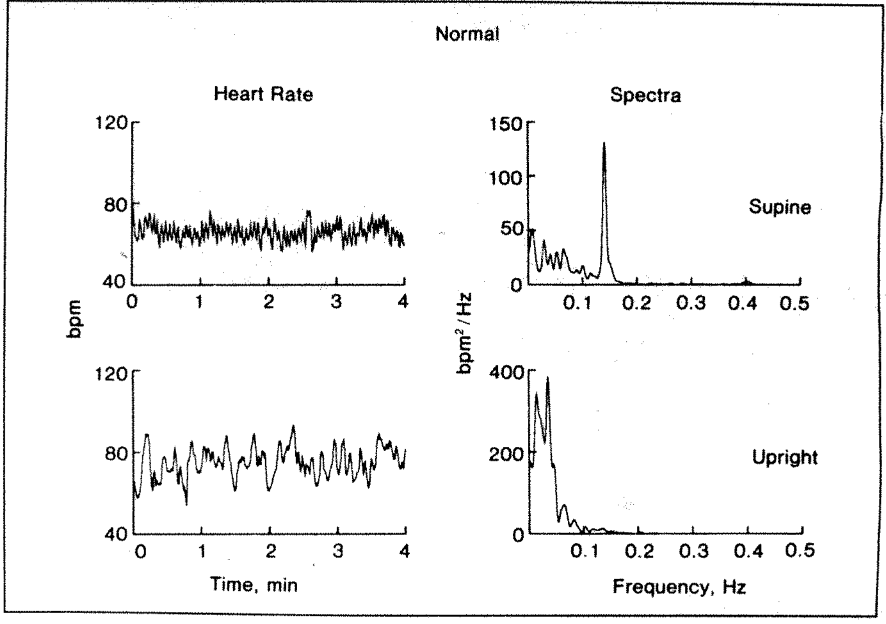

Fig 1.—The power spectrum of the normal resting heart rate. bpm indicates beats per minute.

Table 1.—Summary of Standard Autonomic Test and Spectral Analysis Results*

	Mean	Range	Control Mean
Standard deviation	2.16 ± 1.4	0.6-4.9	4.2 ± 1.3
E-I ratio	1.15 ± 0.16	1.02-1.56	1.4 ± 0.19
Max − min heart rate	14.1 ± 8.5	4.1-27.6	27.9 ± 9.96
30:15 ratio	1.05 ± 0.11	0.93-1.3	1.19 ± 0.18
Valsalva ratio	1.27 ± 0.29	1.0-2.0	1.54 ± 0.33
Cold pressor	19.29 ± 9.13	5.0-35.0	22.8 ± 20.16
Isometric exercise	9.6 ± 9.9	−6.0-30.0	14.2 ± 11.4
Systolic blood pressure change	−26.8 ± 25.8	−87.0-10.0	−1.6 ± 10.3
Supine low-frequency power	4.35 ± 7.4	0.07-26.6	9.05 ± 8.58
Supine high-frequency power	2.32 ± 4.18	0.05-15.04	3.75 ± 2.90
Supine total power	8.16 ± 13.38	0.21-46.48	16.38 ± 14.05
Tilt low-frequency power	7.35 ± 13.5	0.03-49.55	18.39 ± 8.3

*Results are expressed as mean ± SD. Laboratory control values are included for comparison purposes. E-I indicates expiratory-inspiratory.

The Hemodynamic Response to Standing.—Blood pressure change and heart rate were measured for 5 minutes after active standing. The change in heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure was recorded.[16] The ratio of the longest R-R interval at around the 30th beat to the shortest R-R interval around the 15th beat after active standing was calculated (30:15 ratio).[16]

Specially designed and validated software computed the measurements and ratios described above, and stored all data.

Spectral Analysis Methods

A surface lead of the electrocardiogram was recorded on magnetic tape during spontaneous respiration in the supine and upright positions following passive tilting to 60° on an electrically driven tilt table. After anti-alias filtering, the electrocardiogram was sampled off line at 360 Hz. R-waves were detected, and a smoothed instantaneous heart rate time series was formed at 3 Hz, as previously described.[17] One 3-minute (171 seconds = 512 points) segment of data from each position was chosen for power spectral analysis, which was performed using the Blackman-Tukey method.[18]

The power spectra were quantified by the area (power) in two frequency bands: low-frequency power from 0.02 to 0.15 Hz, and high-frequency power from 0.15 to 1.0 Hz. The fractional power in each band was also computed as a percentage of the total power. Traditional tests predominantly measuring parasympathetic nervous system function were compared with supine, total power, supine high-frequency power, and supine low-frequency power. Traditional tests, predominantly measuring sympathetic nervous system function, were compared with the change in low-frequency power on moving from a supine to an upright position.

Statistical Methods

Multiple linear regression was used to predict standard autonomic test results as a function of age, duration of diabetes, and a spectral analysis index chosen as described above. Independent variables were considered significant if $P < .05$. The following regression equation was used: Autonomic Test Result=Constant+β_1 Spectral Index+β_2 Patient Age+β_3 Duration of Diabetes, where β_i represents the respective coefficients estimated by linear regression. Calculations were made using the SYSTAT Statistical Package (Systat Inc, Evanston, Ill).

RESULTS

Autonomic Tests and Spectral Analysis

The mean, SDs, and range of values obtained on the individual autonomic tests and spectral analysis are displayed in Table 1. For comparison purposes, we have included in this table healthy control subject values for the standard autonomic tests (age and sex matched) and spectral indexes (age range, 28 to 79 years; median age, 54 years).

Power Spectra

A normal power spectrum is displayed in Fig 1, and examples from our case material are displayed in Figs 2 and 3. In Fig 2, showing the power spectrum of a diabetic patient with moderate neuropathy, the decrease in power in both the high and low frequencies is seen in the supine position. The loss of power in all frequencies is noted in Fig 3 showing the power spectrum of the diabetic patient with severe autonomic neuropathy.

Tests of Parasympathetic Function

Supine high-frequency power, supine low-frequency power, and supine total power were significant predictors of the E-I ratio, the Max − Min, the SD, the 30:15 ratio, and the Valsalva ratio. When used in a regression equation in conjunction with the patient's age and duration of diabetes, these spectral indexes predicted a large percentage of the variation in test results (R^2 values between 0.64 and 0.92) (Tables 2 through 4). Patient age was only a significant predictor of the Max − Min and the 30:15 ratio.

This is graphically displayed in Fig 4, where the observed autonomic test result is plotted against the autonomic test result predicted by the regression equation. In this figure, a test with perfect prediction would result in all points lying along a 45° line. Conversely, a test with no predictive value would always yield the mean of the observed sample.

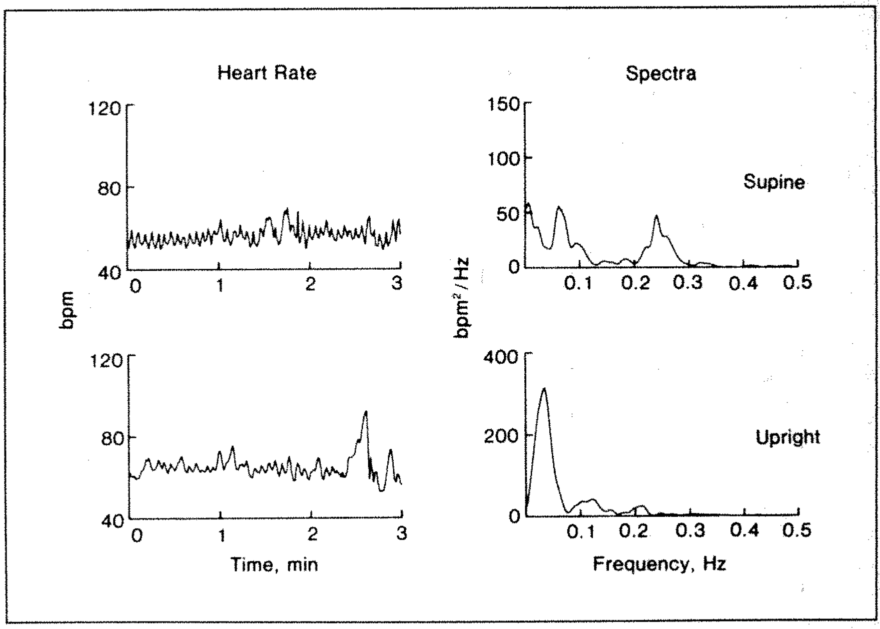

Fig 2.—The power spectrum of the resting heart rate of a diabetic patient with moderate autonomic dysfunction. bpm indicates beats per minute.

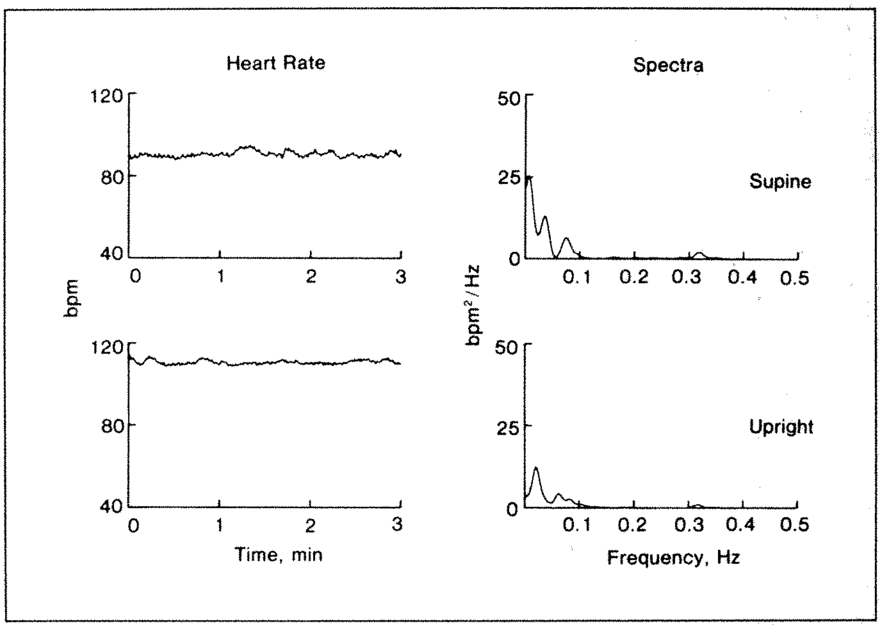

Fig 3.—The power spectrum of the resting heart rate of a diabetic patient with severe autonomic dysfunction. bpm indicates beats per minute. Note the lower *y*-axis scale of the power spectrum.

Table 2.—Linear Regression Analysis Predicting Autonomic Test Results as a Function of Age, Duration of Diabetes Mellitus, and Supine High-Frequency Power*

	E-I Ratio	Max − Min Heart Rate	30:15 Ratio	Valsalva Ratio	SD
Constant	1.074†	18.242†	0.948†	1.221†	1.751‡
Age	−0.001	−0.192‡	0.001‡	−0.001	−0.007
Duration of diabetes mellitus	0.000	0.005	−0.03‡	−0.008§	−0.007
Supine high-frequency power	0.060†	2.606‡	0.066†	0.131†	0.514†
R^2	0.92	0.73	0.90	0.85	0.64

*E-I indicates expiratory-inspiratory.

†$P < .005$.

‡$P < .05$.

§$P < 0.1$.

Tests of Sympathetic Function

The change in low-frequency power on moving from a supine to an upright position, when used in the above regression equation, was a modest predictor of the systolic and diastolic blood pressure fall in response to a postural change. It was a poor predictor of the blood pressure response to isometric exercise and a cold stimulus. Patient age was only a significant predictor of the blood pressure response to isometric exercise (Table 5). The graphic display of the observed autonomic test result plotted against the autonomic test result predicted by the regression equation is shown in Fig 4.

COMMENT

Autonomic dysfunction is a well-documented complication of diabetes presenting with symptoms such as orthostatic hypotension, gastroparesis, impotence, and bowel and bladder dysfunction.[1] The significant associated mortality and morbidity due to silent myocardial ischemia,[19] sudden cardiac death,[20] renal disease,[21] and anesthetic complications[22] emphasize the need for accurate, sensitive, and specific tests of autonomic function.

The standard tests described above provide an indirect measure of autonomic function. Although the physiology of these tests is complex and involves considerable interplay between efferent and afferent divisions of the parasympathetic and sympathetic nervous system, many of these tests are thought to reflect the afferent response to one specific division of the autonomic nervous system. For example, tests of heart rate variation (SD, E-I ratio, and Max − Min), the 30:15

Table 3.—Linear Regression Analysis Predicting Autonomic Test Results as a Function of Age, Duration of Diabetes Mellitus, and Supine Low-Frequency Power*

	E-I Ratio	Max − Min Heart Rate	30:15 Ratio	Valsalva Ratio	SD
Constant	1.149†	20.619†	0.964†	1.297†	2.051‡
Age	−0.002	−0.227‡	0.001	−0.002	−0.012
Duration of diabetes mellitus	−0.001	−0.033	−0.003	−0.009‡	−0.012
Supine low-frequency power	0.882‡	0.019†	0.051†	0.199†	0.199†
R^2	0.65	0.68	0.82	0.86	0.65

*E-I indicates expiratory-inspiratory.
†$P < .005$.
‡$P < .05$.

Table 4.—Linear Regression Analysis Predicting Autonomic Test Results as a Function of Age, Duration of Diabetes Mellitus, and Supine Total Power*

	E-I Ratio	Max − Min Heart Rate	30:15 Ratio	Valsalva Ratio	SD
Constant	1.135†	20.040‡	0.958‡	1.270‡	1.938†
Age	−0.001	−0.220†	0.001	−0.002	−0.011
Duration of diabetes mellitus	−0.001	−0.015	−0.003	−0.008§	−0.008
Supine total power	0.009‡	0.475†	0.010‡	0.027‡	0.106‡
R^2	0.68	0.69	0.81	0.87	0.66

*E-I indicates expiratory-inspiratory.
†$P < .05$.
‡$P < .005$.
§$P < 0.1$.

Fig 4.—Comparison of the observed autonomic test result with the test result predicted by linear regression analysis as a function of age, duration, and specific spectral index. Top row, Results predicted by supine high-frequency power (all four graphs). Bottom row, Results predicted by change in low-frequency power (the first three graphs) and by supine high-frequency power and change in low-frequency power (the fourth graph). See Table 1 footnote for explanation of symbols.

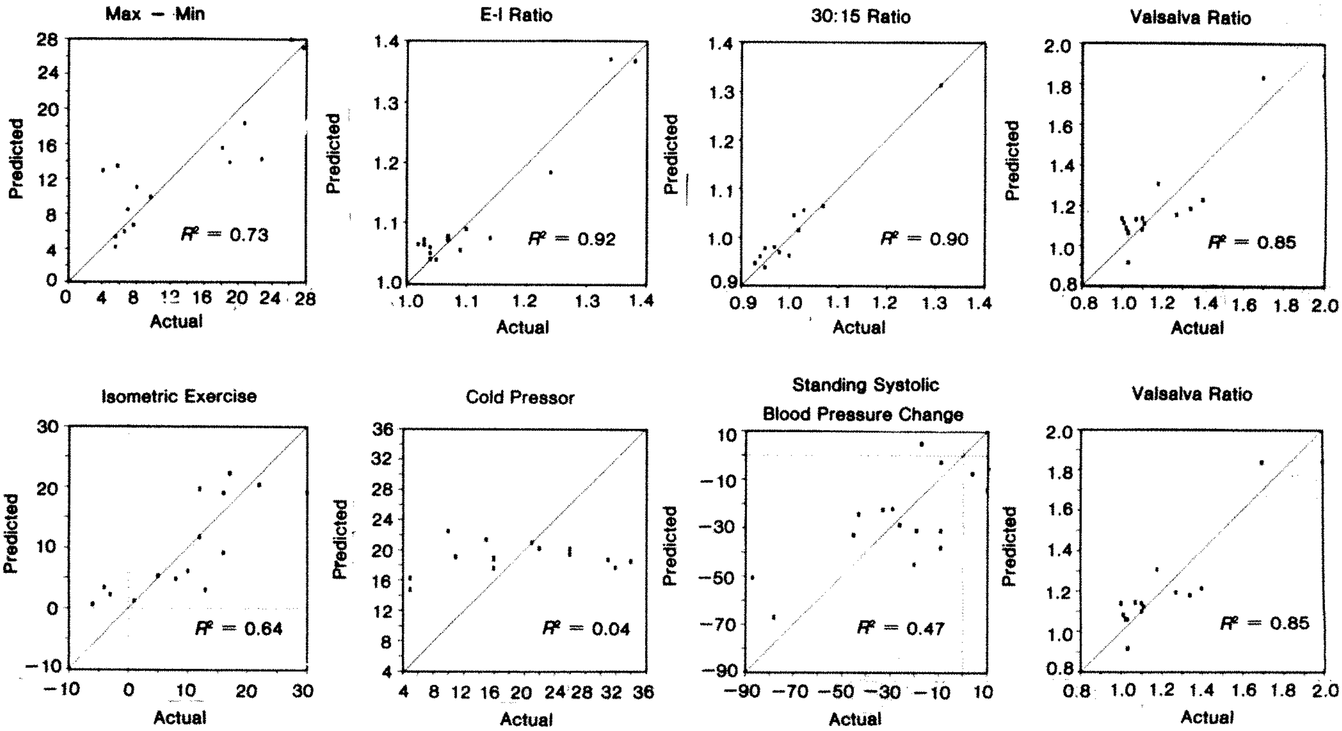

Table 5.—Linear Regression Predicting Autonomic Test Results as a Function of Age, Duration of Diabetes Mellitus, and Change in Low-Frequency Power on Moving From the Supine to Upright Position

	Standing Blood Pressure					
	Systolic	Diastolic	Isometric Exercise	Cold Pressor	Valsalva Ratio	30:15 Ratio*
Constant	−25.746	−14.315	−9.294	24.387†	1.462†	1.073‡
Age	0.129	0.067	0.413‡	−0.058*	−0.004	−0.000
Duration of diabetes mellitus	−1.4206*	−0.210	0.151	−0.166	−0.012	−0.005
Change in low-frequency power	−86.496*	−53.140†	−6.162	11.320	−0.772	−0.103
R^2	0.47	0.37	0.64	0.04	0.49	0.20

*$P < .1$.
†$P < .05$.
‡$P < .005$.

ratio, and the Valsalva ratio are regarded predominantly as measures of the parasympathetic nervous system, while the blood pressure response to postural change, exercise, and cold are believed to predominantly reflect activity of the sympathetic nervous system.[2] Recent publications have drawn attention to the insensitivity of these tests to early alterations in sympathetic function.[3] Furthermore, the need for active patient participation, that is often unstandardized, decreases the reproducibility of these tests.

This study on a group of diabetic subjects with symptoms of autonomic dysfunction supports the use of spectral analysis of heart rate as a measure of autonomic function across the range of values associated with autonomic failure. Earlier reports have characterized the power spectrum of heart rate variation in animals,[4] normal human subjects,[5] and patients with congestive heart failure,[21] near-miss sudden infant death syndrome,[23] sudden cardiac death,[24] cardiac transplants,[25] and acute myocardial infarction.[26] In a group of diabetic subjects, Lishner et al[27] demonstrated a decline in power in all frequency ranges in comparison with those of control subjects. Pagani et al[28] demonstrated reduced R-R variance at rest and a significant difference between the increase in low-frequency power and decrease in high-frequency power in response to tilt in a group of diabetic patients compared with control subjects. These studies included only small numbers of patients with signs or symptoms of autonomic dysfunction and did not compare spectral analysis with individual tests of autonomic function.

Prior works[5-7] have demonstrated that vagus nerve activity mediates low-frequency power, high-frequency power, and total power, particularly in the supine position. We, therefore, regarded those supine spectral indexes as measures of parasympathetic function and compared them with traditional tests of the parasympathetic nervous system. In this study, those spectral indexes were significant predictors of the tests of heart rate variation measuring parasympathetic cardiac function. These tests included the standard deviation of heart rate—a measure of the spread around the mean heart rate, and the Max − Min and E-I ratio—measures of the amplitude of the heart rate variation during controlled respiration. Our results are consistent with prior works[5-7] delineating the role of the vagus nerve as a mediator of oscillations in heart rate in both high- and low-frequency bands and support the use of spectral analysis as a test of parasympathetic nervous system function in this population group.

Power in the low-frequency band forms the dominant component of the heart rate power spectrum in standing subjects,[5,28] following acute hemorrhage,[29] in patients with congestive heart failure,[23] and in patients after recent myocardial infarction.[27] These are all states associated with an increase in sympathetic outflow to the sinus node. Furthermore, the move from the supine to the upright position, which is associated with increased sympathetic nervous system outflow,[30] produces a shift in spectral power from high- to low-frequency bands. This shift in spectral power is reduced by β-adrenergic receptor blockade.[5] We, therefore, used the change in low-frequency spectral power occurring after tilting as an index of sympathetic nervous system activity. The change in low-frequency power on moving from supine to upright position was a modest predictor of the blood pressure fall in response to postural change. The change in low-frequency power was not a significant predictor of the blood pressure response to isometric exercise or to a cold stimulus. This, however, may be a reflection of the insensitivity or inaccuracy of the traditional tests themselves. It is of interest in this regard that patient age was a significant predictor of the isometric exercise test result (Table 5).

The cardiovascular physiology brought into play in response to a Valsalva maneuver or an active postural change involves a complex interplay between muscular activity, low- and high-pressure baroreceptors, the sympathetic nervous system efferents to the peripheral vascular tree, and the parasympathetic cardiac efferents.[30,31] Nevertheless, the Valsalva ratio and the 30:15 ratio (a measure of the heart rate response to postural change) are regarded primarily as indexes of parasympathetic cardiac function. These ratios are a measure of the sequential heart rate response to specific physiological perturbations, although they do not measure beat-to-beat heart rate variation. In our study, those ratios correlated strongly with spectral indexes measuring parasympathetic function and those indexes were able to accurately predict the Valsalva ratio and 30:15 ratio test results. The change in low-frequency power, a proposed measure of sympathetic nervous system function, was not a significant predictor of the Valsalva ratio and 30:15 ratio in this diseased population. Regressions using multiple spectral measures were attempted in order to incorporate the potential influence of both the sympathetic and parasympathetic nervous system on these test results (Fig 4). None of these regression equations were significantly superior predictors of autonomic test results to the regression equations containing a single spectral measure.

There is no single accepted gold-standard measure of autonomic dysfunction, although in recent years a battery of tests has gained widespread acceptance in assessing the autonomic nervous system. Without such a standard, the direct comparison between two different tests is of limited value since there is no reliable way of assessing which result is correct when the tests disagree. Discordance in test results may reflect lack of accuracy in either test. However, assuming that the standard test result correlates with the underlying disease process being measured, then, as a minimal criterion of value, the new test should correlate with the standard test. This study, comparing power spectral analysis with standard tests of autonomic function, provides support for the use of heart rate spectral analysis as a clinical test of autonomic function in patients with known or suspected autonomic dysfunction. Spectral indexes correlated strongly with, and were significant predictors of, several traditional tests of autonomic nervous system function. The minimal patient cooperation required to carry out this test and the possibility of deriving indexes of both sympathetic and parasympathetic nervous system functions from a single test may well outweigh the fact that sophisticated (but increasingly available) computer techniques are required to perform spectral analysis.

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References

1. Ewing DJ, Clark BF. Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab.* 1986;15:855-888.
2. Ewing DJ. Practical bedside investigation of diabetic autonomic failure. In: Bannister R, ed. *Autonomic Failure.* Oxford, England: Oxford University Press; 1983:371-405.
3. Low PA, Zimmerman BR, Dyck PJ. Comparison of distal sympathetic with vagal function in diabetic neuropathy. *Muscle Nerve.* 1986;9:592-596.
4. Akselrod S, Gordon D, Ubel FA, Shannon DC, Barger AC, Cohen RJ. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. *Science.* 1981;213:220-222.
5. Pomeranz B, Macaulay RJB, Caudill MA, et al. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol.* 1985;248:H151-H153.
6. Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol.* 1985;249:H867-H875.
7. Warner HR, Russell RO. Effects of combined sympathetic and vagal stimulation on heart rate in the dog. *Circ Res.* 1978;24:567-573.
8. Gundersen HJG, Neubauer B. A longterm diabetic autonomic abnormality. *Diabetologia.* 1977;13:137-140.
9. Ewing DJ, Borsey DQ, Bellavere F, Clark BF. Cardiac autonomic neuropathy diabetes: comparison of measures of R-R interval variation. *Diabetologia.* 1981;21:18-24.
10. Sundkvist G, Almer LO, Lija B. Respiratory influence of the heart rate in diabetes mellitus. *BMJ.* 1979;1:924-925.
11. Ewing DJ. Cardiovascular reflexes in autonomic neuropathy. *Clin Sci Mol Med.* 1978;55:321-327.
12. Levin AB. A simple test of cardiac function based upon the heart rate changes induced by the Valsalva maneuver. *Am J Cardiol.* 1966;18:909-999.
13. Hines EA, Brown EGE. The cold pressor test for measuring the reactibility of the blood pressure: data concerning 571 normal and hypertensive patients. *Am Heart J.* 1936;11:1-9.
14. Hume L, Ewing DJ, Campbell IW. Heart rate response to sustained hand grip. *Clin Sci.* 1979;56:287-291.
15. Sundkvist G, Lija B, Almer LO. Abnormal diastolic blood pressure and heart rate reaction to tilting in diabetes mellitus. *Diabetologia.* 1980; 19:433-438.
16. Ewing DJ, Campbell IW, Murray A, et al. Immediate heart rate response to standing. *BMJ.* 1978;1:145-147.
17. Berger RD, Akselrod S, Gordon D, Cohen RJ. An efficient algorithm for spectral analysis of heart rate variability. *IEEE Trans Biomed Eng.* 1986;33:900-904.
18. Blackman RB, Tukey JW. *The Measurement of Power Spectra From the Point of View of Communications Engineering.* New York, NY: Dover; 1959.
19. Faerman I, Faccio E, Milei J, et al. Autonomic neuropathy and painless myocardial infarction in diabetic patients. *Diabetes.* 1977; 26:1147-1158.
20. Page MM, Watkins PJ. Cardiorespiratory arrest in diabetic autonomic neuropathy. *Lancet.* 1978;1:14-16.
21. Ewing DJ, Campbell IW, Clark BF. The natural history of diabetic autonomic neuropathy. *QJMed.* 1980;193:95-108.
22. Saul JP, Arai Y, Berger RD, Lilly LS, Colucci WS, Cohen RJ. Assessment of autonomic regulation in chronic congestive heart failure by heart rate spectral analysis. *Am J Cardiol.* 1988; 61:1292-1299.
23. Gordon D, Cohen RJ, Kelly D, Akselrod S, Shannon DC. Sudden infant death syndrome: abnormalities in short-term fluctuations in heart rate and respiratory activity. *Pediatr Res.* 1984; 18:921-926.
24. Meyers GA, Martin GJ, Magid NM, et al. Spectral analysis of heart rate variability in sudden cardiac death: comparison to other methods. *IEEE Trans Biomed Eng.* 1986;33:1149-1156.
25. Sands KEF, Appel ML, Lilly LS, Schoen FJ, Mudge GH, Cohen RJ. Power spectrum analysis of heart rate variability in human cardiac transplant recipients. *Circulation.* 1989;79:76-82.
26. Lombardi F, Sandrone G, Pruner S, et al. Heart rate variability as an index of sympathovagal interaction after acute myocardial infarction. *Am J Cardiol.* 1987;60:1239-1245.
27. Lishner M, Akselrod S, Moore A, Vroz O, Divon M, Ravid M. Spectral analysis of heart rate fluctuations: a noninvasive, sensitive method for the early diagnosis of autonomic neuropathy in diabetes mellitus. *J Auton Nerv Syst.* 1987;19:119-125.
28. Pagani M, Malfatto G, Pierini S, et al. Spectral analysis of heart rate variability in the assessment of autonomic diabetic neuropathy. *J Auton Nerv Syst.* 1988;23:143-153.
29. Madwed JB, Sands KEF, Saul JP, Cohen RJ. Spectral analysis of beat-to-beat variability in HR and ABP during hemorrhage and aortic constriction. In: Lown B, Malliani A, Prosdocimi M, eds. *Neural Mechanisms and Cardiovascular Disease.* Padova, Italy: Liviana Press; 1986;5:291-301.
30. Burke D, Sundlof G, Wallin BG. Postural effects on muscle sympathetic activity in man. *J Physiol.* 1977;272:393-414.
31. Eckberg D. Parasympathetic cardiovascular control in human disease: a critical review of methods and results. *Am J Physiol.* 1980; 239:H581-H593.

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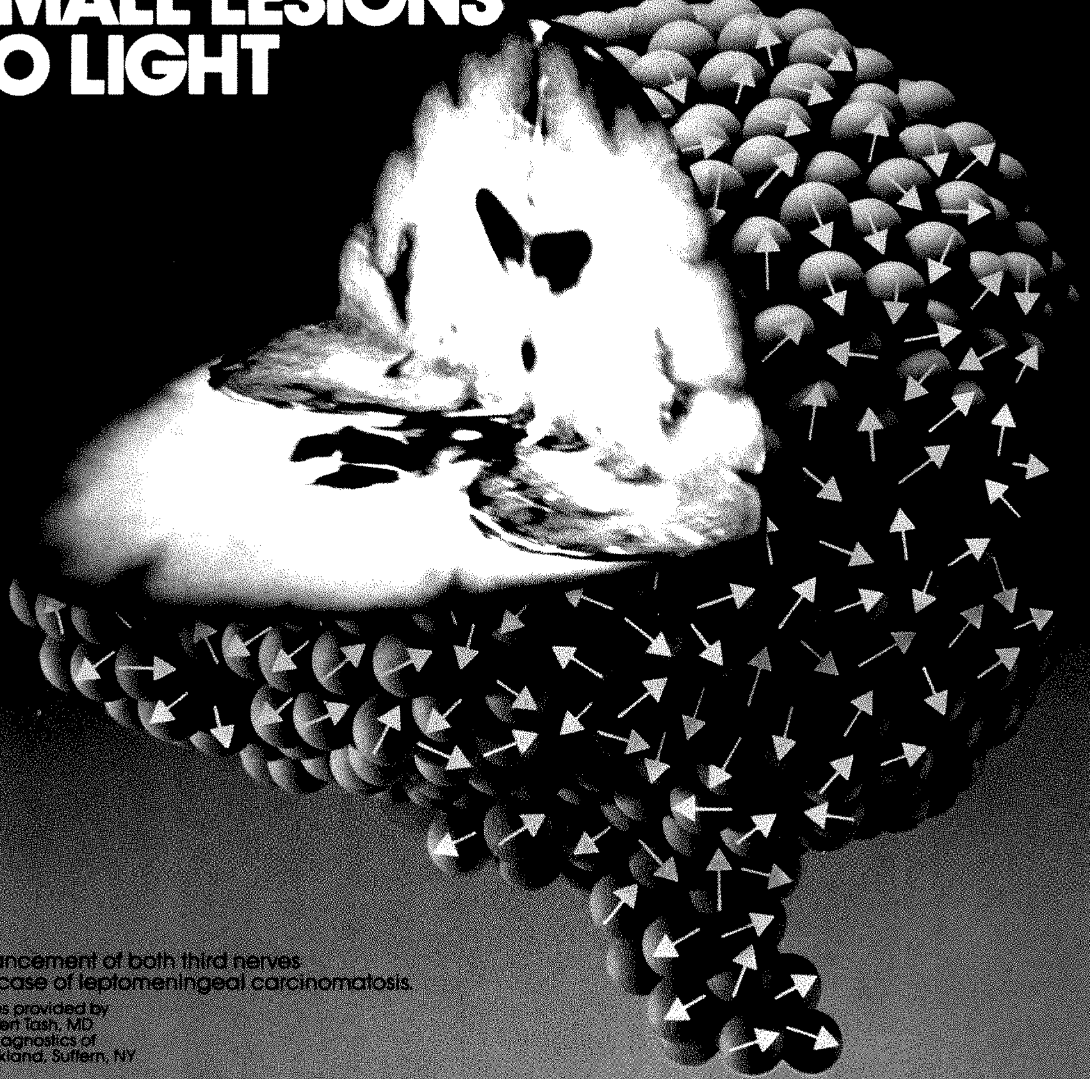

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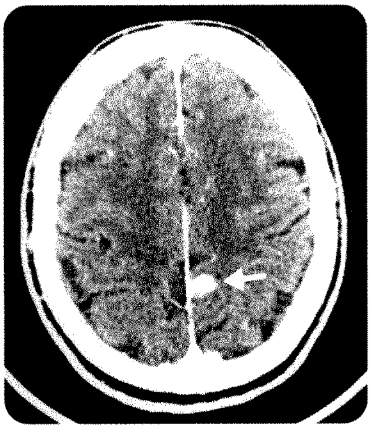

Figure 1. Contrast CT scan shows a circumscribed lesion in left parasagittal region (arrow), consistent with either metastasis or meningioma.

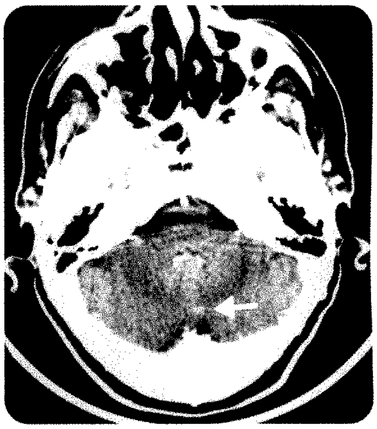

Figure 2. Contrast CT scan through posterior fossa suggests punctate area of contrast uptake in the vermis (arrow).

MRI ALONE WAS NOT DIAGNOSTIC

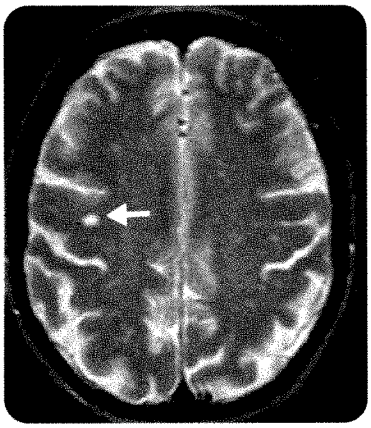

Figure 3. T2-weighted (TR 2000/TE 80) image shows area of high signal intensity in right frontoparietal region (arrow). Differential considerations include metastasis, small infarct, and demyelination. The lesion in left parasagittal region, seen in Figure 1, is not visualized.

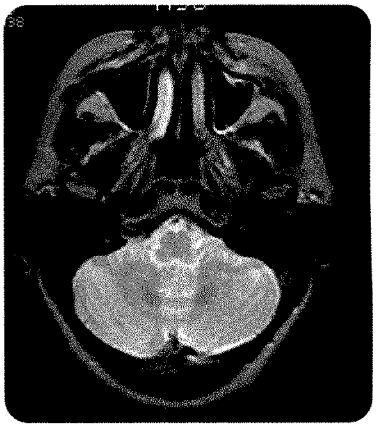

Figure 4. T2-weighted (TR 2000/TE 80) image through posterior fossa shows no abnormalities.

MAGNEVIST® INJECTION: A CRITICAL STEP IN DETECTING BRAIN METASTASES

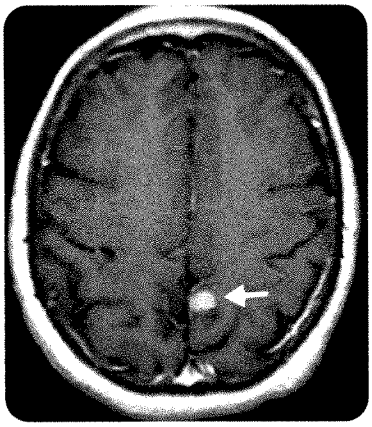

Figure 5. T1-weighted (TR 600/TE 30) image after MAGNEVIST® injection shows an enhancing lesion in left parasagittal region (arrow), as in Figure 1. The high-signal intensity lesion seen in Figure 3 does not enhance. This finding is consistent with chronic small-vessel ischemic disease, not with metastatic disease.

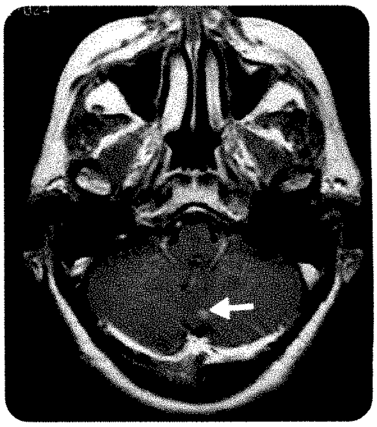

Figure 6. T1-weighted (TR 600/TE 30) enhanced image taken through posterior fossa shows well-delineated lesion in the inferior aspect of the vermis (arrow). Lesion was not clearly appreciated on unenhanced MRI or contrast CT studies.

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☐ INCREASES DETECTION OF INTRACRANIAL LESIONS

May detect additional and often smaller lesions than seen with either contrast-enhanced CT or unenhanced T2-weighted images[1,2]

☐ DETECTION OF ADDITIONAL LESIONS MAY ALTER THERAPY

MAGNEVIST® injection can increase the radiologic suspicion of metastatic disease, reveal locations more favorable for biopsy, prompt the search for a primary tumor, and modify therapeutic objectives and methods[3]

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

BETTER MEDICINE THROUGH BETTER IMAGES

BERLEX
IMAGING®

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.

Well tolerated[4] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCES: 1. Hinshaw DB Jr, Hasso AN. Gd-DTPA enhances MRI of central nervous system. *Diagnostic Imaging*. 1989;11:90-99. **2.** Price AC, Runge VM, Nelson KL. CNS—neoplastic disease. In: Runge VM, ed. *Enhanced Magnetic Resonance Imaging*. St. Louis: CV Mosby Company; 1989:139-177. **3.** Healy ME, Hesselink JR, Press GA, Middleton MS. Increased detection of intracranial metastases with intravenous Gd-DTPA. *Radiology*. 1987;165:619-624. **4.** Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 μg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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60621-6 Revised 7/90

Treatment of Multiple Sclerosis With Hyperbaric Oxygen

Results of a National Registry

Eric P. Kindwall, MD; Michael P. McQuillen, MD; Bhupendra O. Khatri, MD;
Harvey W. Gruchow, PhD; Marilyn L. Kindwall, MS

• Three hundred twelve patients were entered into a long-term study of effects of hyperbaric oxygen on multiple sclerosis. The protocol called for an initial 20 treatments in either the monoplace or multiplace chamber on a daily basis followed by monthly booster treatments for 2 years. One hundred seventy neurologists and 22 institutions provided data for this study. There was no control group, but the study was based on Schumacher's postulation that a scientifically valid study to test the efficacy of a new therapy was possible by choosing patients who were definitively diagnosed with multiple sclerosis and following them up for 2 years after the imposed treatment. If the overwhelming majority of the subjects failed to get worse over the 2-year observation period, the efficacy of the treatment would be manifest. The expanded Kurtzke Disability Status Scale (EDSS) was used to assess the severity of the disease state. The dropout rate was high with only 76% (237 of 312 patients) finishing the initial 20 treatments. Twenty-two percent (69 of 312) finished 1 year of booster therapy, and 9% (28 of 312) completed 2 years of monthly boosters. The mean deterioration on the Kurtzke EDSS score was 0.93 or almost a full step from the beginning of treatment until the last evaluation. There was no difference in outcome between those who had the shortest and longest periods of time between onset of symptoms and hyperbaric oxygen treatment. Treatment pressure made no difference in outcome. Changes in the Kurtzke EDSS score bore no relationship to the use of booster treatment. Patients who were reasonably well off at the onset of treatment with initial Kurtzke EDSS scores of 1 or 2 ($n = 21$) deteriorated by an average of 1.7 Kurtzke points. Those patients whose initial Kurtzke EDSS scores were greater than 2 ($n = 164$) deteriorated on an average of 0.82 points. Of interest was that 19.5% (39 of 200) of the patients reported a temporary improvement in bladder function, but improvement was maintained in only 11 patients (5.5%) at 2-year follow-up. Fifteen patients (7.5%) indicated long-term worsening. There was no significant change in the working status of the patients following hyperbaric oxygen treatment. Although this study treated the patients in accordance with protocols reported to produce a benefit in multiple sclerosis, we were unable to substantiate any useful long-term effect of hyperbaric oxygen therapy.

(*Arch Neurol.* 1991;48:195-199)

Starting in 1978, anecdotal reports that multiple sclerosis benefited from treatment with hyperbaric oxygen (HBO) heightened interest in this form of treatment among patients and neurologists alike. Treated cases were reported from the United States, Italy, Czechoslovakia, the United Kingdom, Sweden, and Brazil.[1-4]

Although the mechanism for improvement with HBO treatment was not known, HBO has been shown by Prokop and Grasso[5] to ameliorate experimental allergic encephalomyelitis in guinea pigs. Both survival and delay in time of onset was increased in the treated animals. Warren et al[6] independently confirmed that development of encephalomyelitis in guinea pigs and rats was delayed by up to 34 days after injection of antigen when animals immediately began treatment with HBO at 2 atmospheres absolute (ATA).

In 1983, the *New England Journal of Medicine* published the study by Fischer et al,[7] in which 40 patients with advanced chronic multiple sclerosis were randomly divided into an HBO treatment group and a group that received a 10% oxygen mixture. Both groups were treated at a pressure of 2 ATA for 90 minutes once daily for a total of 20 exposures. "Objective improvement" (defined as change in the Kurtzke Disability Status Scale, a functional-system scale, and a fatigability scale) occurred in 12 of 17 patients treated with HBO and in only one of 20 patients treated under normoxic conditions ($P < .0001$). Even though improvement was short-lived in seven of the treated patients, it was long lasting in five. At the 1-year follow-up, deterioration was noticed in two patients in the HBO group and in 11 of the patients in the normoxic group ($P < .0008$).

Because patients began to flock to HBO centers for treatment after the appearance of the article by Fischer et al, it was imperative that a study be devised to gather meaningful data from the treatment results of these patients. Schumacher[8] postulated that a scientifically adequate pilot study was possible without the use of a control group by choosing patients who were pursuing a downhill course, or those who had experienced serious exacerbations, with following up the patients for 2 years after the imposed treatment. If 90% to 100% of such patients failed to get worse, the efficacy of the treatment would be manifest. It was clear that data obtained from a long-term uncontrolled study would be crude compared with those derived from strictly controlled double-blind studies. Therefore, a more rigorous

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Table 1.—Kurtzke Expanded Disability Status Scale Scores

Score	Description
0.0	Normal
1.0	No disability, minimal signs, eg, vibratory decrease, Babinski's sign
2.0	Minimal disability, eg, slight gait, sensory, visuomotor disturbances
3.0	Moderate disability, although fully ambulatory, eg, monoparesis, moderate ataxia, or combination of lesser dysfunction
4.0	Relatively severe disability, although fully ambulatory and able to be self-sufficient and up and about for some 12 h a day Able to walk without aid or rest about 500 m (5 blocks)
4.5	Able to walk without aid or rest about 300 m (3 blocks)
5.0	Disability severe enough to preclude ability to work a full day without special provisions Able to walk without aid or rest about 200 m
5.5	Able to walk without aid or rest about 100 m
6.0	Constant assistance (unilateral, cane, crutch, brace) is required to walk about 20 m without resting
6.5	Constant assistance (bilateral, walker, canes, crutches) is required to walk about 20 m without resting
7.0	Unable to walk beyond 5 m (even with aid); essentially restricted to wheelchair (some 12 h a day); wheels self; transfers alone
7.5	Unable to take a few steps; restricted to wheelchair; needs help in transfer; can operate motorized wheelchair only
8.0	Essentially restricted to bed, but may be out of bed itself much of the day; retains many self-care functions; effective use of arms
8.5	Restricted to bed much of the day; some effective use of arms; retains some self-care functions
9.0	Helpless bed patient; can communicate and eat
9.5	Totally helpless; unable to communicate effectively
10.0	Death due to multiple sclerosis

definition of *benefit* had to be applied to achieve some validity. In order to meet Schumacher's criteria for evidence of therapeutic benefit, favorable results would rest on prevention of exacerbation or of further progression of the disease in an overwhelming majority of subjects over a 2-year period of observation. Using a format based on Schumacher's criteria, we created a registry of HBO-treated patients and embarked on a 3-year prospective study of the effects of HBO in the treatment of multiple sclerosis. The study commenced in February 1983 and ended in January 1987. A total of 22 institutions with hyperbaric treatment facilities contributed the data on which this study is based.

PATIENTS AND METHODS

Registry Membership

Participation in this study was restricted to only those centers that could meet all of the registry protocol eligibility criteria as outlined below. The Registry protocol required that:

1. Only those institutions having an Institutional Review Board designed and functioning under the National Institutes of Health, Bethesda, Md, guidelines could participate in the Registry.
2. The protocol be approved by each participating hospital's Institutional Review board.
3. No professional charges were to be made to the patient. Hyperbaric chamber charges could be charged to the patient but were to be out-of-pocket costs only, presuming it was possible to break this figure out of total operational costs. Provisionally, some insurance companies paid for treatment out of enlightened self-interest.
4. Each patient had to agree to remain in the Registry at least 2 years barring unforeseen circumstances.
5. Patients could only enter the protocol through referral by their neurologists. All neurologic evaluations had to be carried out by Board eligible or Board certified neurologists. All patients with multiple sclerosis treated with HBO at a participating institution had to be entered into the Registry. All patients had to sign an informed consent before entering the Registry.

The Registry data were maintained by the Biostatistical Department at the Medical College of Wisconsin in Milwaukee.

Patient Selection

Only those patients with clinically definite multiple sclerosis and with no contraindications to HBO therapy were allowed to participate in the study. There were no age limitations.

HBO Treatment Protocols

The protocol called for 20 initial treatments on a once-daily basis at least 5 days each week, followed by monthly booster treatments for 2 years. Other than to set limits for reasons of oxygen toxicity, the protocol did not stipulate the HBO treatment pressures rigidly. This was by intent as there had been no study published that had conclusively established an optimal protocol. No facility was permitted to administer oxygen at a pressure greater than 3 ATA and at that pressure for no longer than 90 minutes. In the available literature, treatment pressure has ranged between 1.5 and 3 ATA and treatment has been carried out in both multiplace and monoplace chambers. Institutions were urged to use one of the protocols that had already appeared in the literature as reporting to produce "benefit" as it was felt that only in this way could it be determined which method could prove or disprove the long-term usefulness of existing protocols.

Clinical Evaluation

The severity of the patient's disability was graded using the expanded Kurtzke Disability Status Scale (EDSS) as shown in Table 1. All patients were examined at entry, after 20 HBO treatments, and at 6, 12, 18, and 24 months while they received monthly booster HBO. Standardized evaluation and eligibility forms were sent to all participating institutions.

Chamber Equipment

Patients in this study were treated in either multiplace or monoplace chambers. In the multiplace chambers, masks were generally of the tight-fitting double-seal oronasal aviator type or the patient used a tightly sealed Duke head tent with adequate oxygen flow. At 2 ATA with a perfect mask fit, a Pa_{O_2} should approach 1200 mm Hg. In a monoplace chamber, this is not a problem as the patient's FI_{O_2} is guaranteed to be 100% as the chamber is pressurized with pure oxygen.

Concomitant Management of Patients

Patients were continued on whatever therapeutic regimen they had been receiving prior to entry into the study, including physical therapy. Because of a tendency for corticotropin or corticosteroids to aggravate oxygen toxicity, it was urged that such medications be tapered and stopped prior to beginning HBO treatment. The same applied to baclofen, which is an analogue of γ-aminobutyric acid. The HBO is known to disrupt γ-aminobutyric acid metabolism. Prednisone had been used by 196 (51.2%) of patients at some time; 103 (26.9%) had taken corticotropin. Only three (0.8%) of the patients continued to take steroids during the study. One patient continued with unspecified immunotherapy during HBO treatment.

Complications

No seizures were reported. Thirty-nine patients (10.2%) mentioned "complications" after the first 20 treatments; over 90% of these involved simple ear or sinus discomfort. Occasional nausea was recorded. No cases of blindness were reported.

Statistical Analysis

Standard statistical methods were used for analysis. The independence of frequency distributions was tested with the χ^2 statistic. Mean values were compared between groups using the two-sample t test and an analysis of variance. Associations between two continuous variables were assessed by the Pearson correlation coefficient. Analyses were carried out using the Statistical Program for Social Science software, release 3.0 for the Micro VAX II Computer (Digital Equipment Co, Maynard, Mass).[9]

Table 2.—Clinical Outcome Following Hyperbaric Oxygen Treatment

	Mean Kurtzke EDSS Score (SD)*			
	At Entry	After 20 HBO Treatments	2-y Follow-up	Deterioration
All patients	5.5 (2.0) (n = 312)	5.4 (2.1) (n = 239)	6.4 (2.0)	+0.93 (1.44)†
Patients with follow-up	5.5 (2.1) (n = 185)	5.5 (2.1) (n = 146)	6.4 (2.0) (n = 200)	+0.93 (1.44)† (n = 185)

*EDSS indicates expanded Disability State Scale; HBO, hyperbaric oxygen.
†$P = .01$

Table 3.—Results According to Disease Type*

	Mean Kurtzke EDSS Score (SD)			
Type of Multiple Sclerosis	At Entry	After 20 HBO Treatments	2-y Follow-up	Deterioration
Chronic stable (n = 41)	5.4 (2.2)	5.0 (2.4)	5.9 (2.4)	+0.5 (1.2) (n = 38)
Chronic progressive (n = 156)	5.9 (1.8)	5.9 (1.9)	6.9 (1.7)	+1.0 (1.4)† (n = 24)
Relapsing remitting (n = 23)	3.5 (1.8)	3.4 (2.0)	4.7 (2.1)	+1.3 (2.0) (n = 22)

*EDSS indicates expanded Disability State Scale; HBO, hyperbaric oxygen.
†$P < .01$; for all other differences, P is not significant.

RESULTS

Three hundred eighty-three patients were logged into the study; initial complete data were received on 317 patients, of whom 312 (81.4%) actually received the treatment. All the patients included in the study had enough criteria to confer a definite diagnosis of multiple sclerosis. Thirty-five percent of the patients were male and 65% were female. The mean age at entrance to the study was 43.7 years (range, 18 to 70 years). The mean age at diagnosis was 35 years (range, 12 to 59 years); mean age at onset of symptoms was 32 years (range, 10 to 59 years); and median age at onset of symptoms was 31 years, while the median age for diagnosis was 34 years.

Each patient was referred by a neurologist with the evaluation form being completed by the same physician. There were a total of 170 neurologists who referred patients to the study and who performed evaluations. As with any large study that involved multiple physicians over a period of years, complete information was not received on all patients as the neurologists sometimes left portions of the questionnaire uncompleted or, in some instances, information was not available. For this reason, the number of patients will be found to vary in the analyses. For those 239 patients on whom pressure data for the initial series of treatments were available, 13.6% were treated exclusively at 1.5 ATA, 19.6% were treated at pressures varying between 1.5 and 2 ATA, 58% were treated at 2 ATA, and 7.7% were treated at 2.4 ATA. One hundred ninety-seven patients (51.3%) were treated in multiplace chambers and 139 (44.5%) in monoplace units. For 13 patients (4.2%), this information was not provided. Of the 312 patients who began HBO therapy, 209 (67%) were diagnosed as chronic progressive, 39 patients (12.5%) were chronic stable and 64 patients (20.5%) carried relapsing remitting diagnosis. Two hundred eighty-three patients (90.7%) underwent at least one of the initial 20 HBO treatments; 120 patients (38.5%) finished 6 months of booster treatments; 69 patients (22.1%) finished 12 months, and 37 patients (11.9%) finished 18 months of booster treatments. The number of patients who completed a full 2 years of monthly booster treatments was 28 (9%). Because of a large number of dropouts, the loss of interest on the part of both patients and neurologists, it was not possible to carry out all evaluations as scheduled. Therefore, at the end of the study, it was necessary to contact 200 of the patients by telephone to gather data on final outcome. The purpose of this telephone survey was to fill in gaps in the data, and to determine the patient's final Kurtzke EDSS score by self-assessment and his/her life status. (The overall agreement between patient's self-assessment and the neurologist's score on the Kurtzke scale is 0.93, according to Scheinberg et al.[10])

Table 2 shows the mean Kurtzke EDSS scores at entry, after 20 HBO treatments, and at 2-year follow-up. In the 185 patients for whom both initial and final Kurtzke EDSS scores were obtained by the evaluating neurologist, the mean deterioration in the Kurtzke EDSS score was 0.93 or almost a full step from the beginning of treatment until the last evaluation, 2 years later. Follow-up data on the rest of the patients was obtained by calling them and assigning a Kurtzke EDSS score based on their description of their condition. There was no significant difference in outcome between those who had the shortest period of time between onset of symptoms and initiation of HBO and those who had the longest time between those two historical points ($P = .9599$).

Table 4.—The Role of Booster Therapy

	Mean Kurtzke EDSS Score (SD)*		
Patients	At Entry	2-y Follow-up	Deterioration
Receiving boosters	5.3 (2.1) (n = 192)	6.1 (2.1) (n = 110)	+0.93 (1.5)† (n = 102)
Not receiving boosters	5.7 (1.9) (n = 170)	6.8 (1.9) (n = 90)	+0.93 (1.4)† (n = 83)

*EDSS indicates expanded Disability State Scale.
†P not significant.

Table 3 summarizes the effect of HBO therapy on patients with different forms of multiple sclerosis. Deterioration in the mean Kurtzke EDSS score occurred in all these groups; however, this was significant ($P < .01$) only in the chronic progressive group of patients. As shown in Table 4, it was of no clinical significance whether the patients did or did not receive booster treatments after the completion of initial HBO therapy. At 6 months, changes in EDSS scores were unrelated to the number of boosters ($P = .29$). Of 28 patients who completed 2 years of booster treatments, one had less than once-a-month treatment and three had more than monthly treatments (the maximum being 61 treatments in one patient). The different pressures at which treatments were rendered—either during the initial course (Table 5) or during the booster phase (Table 6)—did not influence the course of disease progression.

Visual Changes

One hundred sixty (80%) of the 200 patients reported no change in vision; 15 (7.5%) experienced temporary im-

Table 5.—Significance of Treatment Pressure in the Initial Course*

	Kurtzke EDSS Score (SD)		
	Initial	Final	Initial to Final Change in Score
Initial treatment pressure			
≤1.75 ATA	5.6 (2.0) (n = 42)	6.9 (2.0) (n = 29)	+0.80 (1.55)† (n = 27)
>1.75 ATA	5.5 (2.0) (n = 112)	6.6 (1.9) (n = 72)	+1.24 (1.34)† (n = 64)

*EDSS indicates expanded Disability State Scale; ATA, atmospheres absolute.
†$P = .17$.

Table 6.—Significance of Booster Treatment Pressure*

	Kurtzke EDSS Score (SD)		
	Initial	Final	Initial to Final Change in Score
Booster treatment pressure			
≤1.75 ATA	5.3 (1.7) (n = 24)	6.2 (1.9) (n = 26)	+0.88† (1.5) (n = 24)
Mixed	4.8 (2.4) (n = 8)	5.9 (2.1) (n = 8)	+0.63† (1.5) (n = 8)
≥2 ATA	5.1 (2.2) (n = 68)	6.2 (2.1) (n = 79)	+1.03† (1.5) (n = 68)

*EDSS indicates expanded Disability State Scale; ATA, atmospheres absolute.
†$P = .73$ (not significant).

provement; 10 (5%) reported lasting improvement; and 15 (7.5%) experienced permanent worsening of vision, following HBO therapy. The HBO itself can cause temporary worsening of myopia and temporary improvement in presbyopia. Usually, these changes spontaneously reverse themselves after 6 weeks. Visual changes are normally seen only after 20 or more closely spaced treatments, typically in patients older than 40 years of age. No cases of blindness or exacerbation of optic neuritis associated with HBO were reported. The authors are aware of one case of complete and permanent blindness with HBO treatment of multiple sclerosis that occurred at another institution prior to the beginning of this study.

Bowel Function

When queried about bowel function, 162 (81%) of 200 patients reported no change, 22 patients (11%) reported temporary improvement, and 5 patients (2.5%) reported lasting improvement. Eleven (5.5%) patients reported a worsening of bowel function that persisted after HBO treatment had been completed.

Bladder Function

Of particular interest were the reports of change in bladder function. Thirty-nine (19.5%) of 200 patients reported temporary improvement in bladder functions; 11 (5.5%) were improved at 2-year follow-up; 15 (7.5%) experienced worsening; and 135 (67.5%) patients reported no change. Changes in bladder function were independent of the changes in Kurtzke EDSS scores.

Working Status

Working was defined as holding a salaried/remunerated job or carrying out of normal housekeeping duties if the patient elected to remain in the home. Forty-four (63.8%) of 69 men and 120 (92%) of 130 women were not working at the start of the study. No significant change was noted in the working status of these patients following HBO treatment.

Improvement Related to Severity

Patients who were reasonably well off at the onset of treatment (initial Kurtzke EDSS scores, 1 or 2; n = 21) deteriorated by an average of 1.7 Kurtzke points, whereas patients whose initial Kurtzke EDSS scores were greater than 2 (n = 164) deteriorated an average of 0.82 points ($P = .03$). Thus, the worse a patient's condition was at the start of HBO, the less the deterioration noted.

COMMENT

There is no benefit from HBO in multiple sclerosis manifest in this study. There is always a possibility that in uncontrolled short-term studies a placebo effect may be apparent. This may have been true in our case as after the initial 20 treatments, there seemed to be a trend toward improvement. However, in other short-term double-blind controlled studies carried out since the publication of the report by Fischer et al,[7] no significant differences were found between the treated patients and the control subjects.[11-17] The placebo response is of great importance when dealing with any therapeutic trial in multiple sclerosis. While the most definitive answer in a clinically variable disorder such as multiple sclerosis can only be obtained through a double-blind controlled therapeutic trial of sufficient duration and with enough patients, the results of this study confirm the negative results of short-term double-blind randomized control studies.

Pallotta et al[4] reported on "good results" in the treatment of six patients. Boschetty and Cernoch[1] reported that the use of HBO in multiple sclerosis led to a "remission of symptoms." Formai et al[2] found that in all their cases the disease was worsening as therapy commenced, but "the changes occurred almost exclusively toward an improvement after several months of observation." They also stated that "the changes associated with or following oxy-hyperbaric treatment could not be confused with those due to clinical fluctuations of the basic illness." Neubauer[3] described the treatment of 250 patients with multiple sclerosis reporting "dramatic" improvement in 39% of the cases and minimal to moderate improvement in 52%. The remainder (9%) showed no change. "Dramatic" improvement was defined as "complete or near total remission." He felt that the best results were seen in patients ill less than 5 years.

Neubauer[3] has stated that pressures in excess of 2 ATA may prove too toxic and may produce further damage to the central nervous system. Yet, Pallotta et al[4] had used 3 ATA and reported good results. Neubauer had initially recommended once- or twice-a-day treatment at 1.5 ATA for 60 to 90 minutes "as tolerated" for the first four treatments, and then 2 ATA for 16 more treatments lasting 60 to 90 minutes "as tolerated" or depending on "clinical response." It was using this protocol that he reported his good results in the treatment of 250 patients. None of the investigators in our study reported any change in "clinical response" during the course of therapy that they could use as an indication for change in treatment pressure, nor were any patients reported "intolerant" to 2 ATA who had "tolerated" 1.5 ATA. Neubauer gave no explanation for the rationale for starting at 1.5 ATA and then going to 2 ATA other than "clinical response."

Using his experience, Neubauer further stated that long-term HBO follow-up is beneficial and that one treatment monthly at 2 ATA was usually sufficient. He also stated that when long-term HBO follow-up is offered, intervals between treatments could be lengthened as much as 3 months. As clinical experience by 1983 had indicated that benefits of HBO treatment might be temporary, booster treatments were included in the protocol at monthly intervals.

Multiple sclerosis is an extraordinarily difficult disease in which to assess the efficacy of any given therapy. Some series[18-20] have reported the placebo response to range from 30% to 80%. Additionally, the disease is often characterized by exacerbations or remissions that can extend over a period of years. For these reasons, control subjects are required in the usual study to document small differences that may be seen in patients treated with any new modality.

It was using the multiplace chamber even with the attendant problem of mask leaks that Fischer reported his good results. Fischer had the impression that those patients whose PaO_2 was at least 1000 mm Hg during treatment did better than did those whose arterial PaO_2 did not reach that level. In the monoplace chamber, high arterial levels of oxygen are guaranteed as the chamber atmosphere is 100% oxygen. We were unable to show differences in outcome, however, referable to the partial PO_2.

There are many who still feel that HBO is a useful modality in the treatment of multiple sclerosis and cite largely uncontrolled statistics to prove their point. Additionally, they now contend that boosters should be given at weekly intervals instead of monthly if results are to be seen. This is despite the fact that *the early highly encouraging reports were based on monthly booster therapy,* and not weekly therapy. We made a good-faith effort to apply HBO treatment in the clinical setting as advocated by its proponents, but it is obvious that from the high number of dropouts and general loss of interest in this modality the patients themselves were not able to recognize the benefits.

It is possible that repeated HBO treatment can provide amelioration on a temporary basis for some symptoms (bladder function, for example), but the cumbersome and expensive nature of this treatment precludes frequent treatment in the usual case. We only required monthly boosters for the purpose of our study, but the majority of the patients could not even comply with that requirement. Thus, it is apparent that, as a mass treatment, HBO therapy has shown itself to be impractical in the US. If we or any of the other centers that conducted short-term, carefully controlled double-blind studies had been able to demonstrate a conclusive benefit for this form of treatment, there would be a good rationale for attempting to construct low-technology monoplace units that could be mass produced and manned by volunteers from the multiple sclerosis community. However, at least in our hands, and based on reports of the double-blind control studies carried out in the United States and the United Kingdom, and elsewhere, this has not been shown to be the case.

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References

1. Boschetty V, Cernoch J. Aplikace kysliku za pretlakeu u nekterych neurologickych onemoceni. *Bratisl Lek Listy.* 1978;53:298-301.

2. Formai C, Sereni G, Zannini D. Hyperbaric oxygen therapy in the treatment of multiple sclerosis. In: *Proceedings of the 4th National Congress of Underwater and Hyperbaric Medicine.* Naples, Italy; 1980.

3. Neubauer RA. Exposure of multiple sclerosis patients to hyperbaric oxygen at 1.5 ATA: a preliminary report. *J Fla Med Assoc.* 1980;67:498-504.

4. Pallotta R, Anceschi F, Costaglioni N, et al. Prospettive di terapia iberbarica nella sclerosis a placche. *Ann Med Navale.* 1980;85:57-62.

5. Prokop L, Grasso R. Ameliorating effects of hyperbaric oxygenation on experimental allergic encephalomyelitis. *Brain Res Bull.* 1978;3:221-225.

6. Warren J, Sacksteder M, Thuning CA. Oxygen immunosuppression: modification of experimental allergic encephalomyelitis in rodents. *J Immunol.* 1978;121:315-320.

7. Fischer BH, Marx M, Reich T. Hyperbaric oxygen treatment of multiple sclerosis: a randomized placebo controlled double-blind study. *N Engl J Med.* 1983;308:181-186.

8. Schumacher GA. Critique of experimental trials in multiple sclerosis. *Neurology.* 1974;24:1010-1014.

9. SPSS Inc. *SPSSX User's Guide 1983,* New York, NY: McGraw-Hill International Book Co; 1983.

10. Scheinberg L, Feldman JF, Ratzker P, et al. The self assessment of neurologic impairments in multiple sclerosis. *Neurology.* 1986;36(suppl 1):284.

11. Barnes MP, Cartlidge NEF, Bates D, et al. Hyperbaric oxygen and multiple sclerosis: short-term results of a placebo-controlled, double-blind trial. *Lancet.* 1985;1:297-300.

12. Erwin CW, Massey EW, Brendle AC, et al. Hyperbaric oxygen influences on the visual evoked potentials in multiple sclerosis patients. *Neurology.* 1985;35(suppl 1):104.

13. Harpur GD, Suke R, Bass BH, et al. Hyperbaric oxygen therapy in chronic stable multiple sclerosis: double-blind study. *Neurology.* 1986; 36:988-991.

14. Hart GB, Rowe MJ, Myers LW, Afifi AA. A controlled study of hyperbaric oxygen treatment in multiple sclerosis. *J Hyper Med.* 1987;1:1-5.

15. Massey, EW, Shelton DL, Pact V, et al. Hyperbaric oxygen in multiple sclerosis: double-blind crossover study of 18 patients. *Neurology.* 1985;35(suppl 1):104.

16. Murthy KN, Maurice PB, Wilmeth JB. Double-blind randomized study of hyperbaric oxygen (HBO) versus placebo in multiple sclerosis (MS). *Neurology.* 1985;35(suppl 1):104.

17. Wiles CM, Clarke CRA, Irwin HP, et al. Oxygen in multiple sclerosis: a double-blind trial. *BMJ.* 1986;292:367-371.

18. Ellison GW, Myers LW, Mickey R, Graves MC, Tourtellotte WW, Nuwer MR. Clinical experience with azathioprine: the pros. *Neurology.* 1988;38(suppl 2):20-23.

19. Johnson K. Treatment of multiple sclerosis with various interferons: the cons. *Neurology.* 1988;38(suppl 2):62-64.

20. Likosky WH. Experience with cyclophosphamide in multiple sclerosis: the cons. *Neurology.* 1988;38(suppl 22):14-18.

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PRECAUTIONS: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

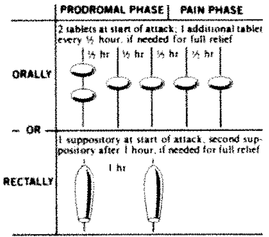
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.



PRODROMAL PHASE
PAIN PHASE
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief
½ hr
½ hr
½ hr
½ hr
ORALLY
— OR —
1 suppository at start of attack, second suppository after 1 hour, if needed for full relief
1 hr
RECTALLY

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Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

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Alterations in Brain Phosphate Metabolite Concentrations in Patients With Human Immunodeficiency Virus Infection

Raymond F. Deicken, MD; Bruno Hubesch, PhD; Peter C. Jensen, MD; Dominique Sappey-Marinier, PhD; Pamela Krell, PhD;
Amy Wisniewski, PhD; Douglas Vanderburg, MD; Reginald Parks, MPH; George Fein, PhD; Michael W. Weiner, MD

• Human immunodeficiency virus (HIV)–infected individuals often demonstrate neuropsychiatric impairment; however, it is unclear how brain metabolism may be altered in such patients. We used in vivo phosphorus 31 magnetic resonance spectroscopy to noninvasively assess brain energy and phospholipid metabolism by measuring brain concentrations of adenosine triphosphate (ATP), phosphocreatine (PCr), and inorganic phosphate (Pi), as well as phospholipid compounds and intracellular pH. In study 1, 17 HIV-seropositive men with varying degrees of neuropsychiatric impairment and six control subjects were studied. Localized spectra were obtained from a heterogeneous 5 × 5 × 5-cm volume of interest (VOI). Patients with HIV infection had a significantly lower ATP/Pi ratio and a trend for a lower PCr/Pi ratio than did the control group. In addition, the ATP/Pi and PCr/Pi ratios were both significantly negatively correlated with overall severity of neuropsychiatric impairment. In study 2, three HIV-seropositive men with neuropsychiatric impairment were compared with 11 HIV-seronegative men. Localized phosphorus 31 magnetic resonance spectra were obtained from two relatively homogeneous VOIs: (1) a predominantly white matter VOI, and (2) a predominantly subcortical gray matter VOI. The three HIV-infected patients demonstrated significantly decreased ATP and PCr concentrations in the white matter VOI. These results suggest that HIV infection of the brain may impair brain cellular oxidative metabolism and that the degree of metabolic compromise may be related to the severity of neuropsychiatric impairment.

(*Arch Neurol.* 1991;48:203-209)

Compelling evidence exists that direct central nervous system (CNS) infection by the human immunodeficiency virus (HIV) occurs in a large proportion of HIV-infected individuals and often results in a neurological syndrome, acquired immunodeficiency syndrome (AIDS) dementia complex (ADC). This complex is characterized by disordered cognition, motor function, and behavior.[1-4] About 75% of autopsies on randomly selected patients with AIDS show CNS pathology,[5] although only about 40% of patients are neurologically symptomatic.[6] Neurologic complications of AIDS may result from diffuse encephalopathy secondary to direct HIV infection of the CNS or from opportunistic CNS infections secondary to the immunosuppressive effects of HIV.[7] Of 30 autopsied adult patients with AIDS,[2] 80% had neurological signs or symptoms and 60% had histopathologic findings of subacute encephalitis; preliminary data using monoclonal antibodies against the p24 antigen in frozen brain tissue showed HIV in the CNS, especially in multinucleated cells. In over 90% of 70 autopsied patients,[1] abnormalities were predominantly located in the white matter and subcortical areas, with relative sparing of the cortex; progressive dementia was present in 46 patients. Human immunodeficiency virus has been detected in the white matter and basal ganglia of eight demented patients[8] and in the cerebral spinal fluid or neural tissue of 11 of 13 patients with AIDS, where subacute encephalopathy, including monocyte/macrophage infiltration, was found.[9] Subacute encephalitis consistent with a viral infection of the CNS was histologically defined in 12 patients with AIDS in whom the white matter was more severely affected than was the gray matter. In most cases, the HIV infection was restricted to capillary endothelial cells, mononuclear cells, and giant cells.[10] In the brains of two patients, it was possible to identify mononucleated and multinucleated macrophages that supported replication of the AIDS retrovirus in brain tissue.[11] In children with AIDS, study of CSF has shown HIV antigen indicating viral expression in the CNS, correlated with the occurrence of progressive encephalopathy.[12] On the basis of culturing HIV from the cerebrospinal fluid, it was concluded that HIV is neurotropic, capable of causing acute meningitis, and responsible for

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From the Infectious Diseases Clinic (Drs Jensen and Krell and Mr Parks), Magnetic Resonance Unit (Drs Deicken, Hubesch, Sappey-Marinier, and Weiner), Psychiatry (Drs Vanderburg and Fein), and Psychology Service (Dr Wisniewski) Veterans Affairs Medical Center, San Francisco, Calif; and the Departments of Medicine (Drs Hubesch, Jensen, Sappey-Marinier, and Weiner), Psychiatry (Drs Deicken and Fein), and Radiology (Drs Hubesch, Sappey-Marinier, and Weiner), University of California, San Francisco.

Read before the Sixth International Conference on AIDS, San Francisco, Calif, June 20-24, 1990.

Reprint requests to Director, Magnetic Resonance Center, Veterans Affairs Medical Center (11M), 4150 Clement St, San Francisco, CA 94121 (Dr Weiner).

AIDS-related chronic meningitis and dementia.[13]

Results of neuroimaging studies have consistently indicated preferential subcortical involvement in HIV infection. Subcortical structures have been shown to be affected to a greater degree than have the cortical structures on positron emission tomographic studies, at least in the initial phases of the syndrome.[14] Magnetic resonance imaging (MRI) of patients with AIDS and patients with the AIDS-related complex (ARC) reveals multiple small and discrete lesions of high signal intensity in subcortical white matter, as well as ventricular and sulcal enlargement that is suggestive of brain atrophy.[15,16]

Navia and colleagues[1] suggested that impaired memory, concentration difficulties, and psychomotor slowing represent the most common early manifestations of ADC. This presentation is similar to that seen in other diseases with primary damage to white matter and subcortical structures.[17] It is on this basis that ADC has been tentatively classified as a subcortical dementia. In this regard, Brouwers et al[18] recently compared the patterns of neuropsychological performance of HIV-infected patients with those of patients with Alzheimer's disease (cortical dementia) and Huntington's disease (subcortical dementia). Discriminant analysis revealed that most patients with HIV were either classified as normal or as having Huntington's disease, while none were classified as having Alzheimer's disease. These results were not secondary to depression in a subset of patients with HIV, since the patients with HIV classified with the patients with Huntington's disease did not differ on the Beck Depression Inventory from those classified as normal. These findings are supported by the work of Van Gorp and colleagues.[19]

In much of the emerging literature on ADC, cognitive impairment is often used synonymously with dementia, with variability across studies both on the criteria for judgment of impairment and the number of affected cognitive domains required for the diagnosis of ADC. A neurobehavioral operational definition of dementia usually includes acquired persistent impairment in at least three of the following spheres of mental activity: psychomotor control, attention and concentration, language, memory, visuospatial skills, emotion, personality, and executive functions such as reasoning or cognitive flexibility. Most of the literature on ADC describes patients with varying degrees of impairment, including patients without a full-blown dementia.

Although research has been considerable on ADC in recent years, the metabolic pathology associated with HIV-related neuropsychiatric impairment is poorly understood. Rottenberg and colleagues[14] studied regional cerebral glucose metabolism with positron emission tomography in nine patients with ADC. They found relative subcortical (thalamus and basal ganglia) hypermetabolism in early ADC, with disease progression accompanied by cortical and subcortical gray matter hypometabolism. Single-photon emission computed tomography of 12 patients with ADC revealed either multiple or focal decreases in blood flow, the latter corresponding to focal neurological signs or symptoms in all but one case.[20] Bottomley et al[21] reported in an abstract that in vivo phosphorus 31 magnetic resonance spectroscopy (MRS) reveals significant reductions in adenosine triphosphate (ATP) and phosphocreatine (PCr) concentrations in eight patients with ADC, compared with control subjects. Finally, Arnold et al[22] reported that patients with a post-viral exhaustion/fatigue syndrome had excessive intracellular acidosis (measured by phosphorus 31 MRS) produced by voluntary exercise of forearm flexor muscle, suggesting that viral infection directly or indirectly produces an impairment of muscle oxidative metabolism. These studies suggest that HIV-related neuropsychiatric impairment may be associated with changes in cerebral blood flow and energy metabolism.

In an effort to further characterize the CNS metabolic alterations associated with HIV-related neuropsychiatric impairment, we utilized in vivo phosphorus 31 MRS. In vivo MRS is used to monitor intracellular metabolites noninvasively and is thought to be free of biological hazard. Moreover, because metabolites may be lost or distorted when tissue is subjected to more traditional biochemical assays such as freeze clamping, MRS may provide a more accurate assessment of concentrations of metabolites free in solution. Phosphorus 31 MRS detects the high-energy phosphates ATP and PCr and their hydrolysis product, inorganic phosphate (Pi). The ratio ATP/Pi is often calculated to indicate the "energy state" of the tissue. Phosphorus 31 MRS also detects signals from phosphodiesters (PDE) and phosphomonoesters (PME), which provide information regarding phospholipid metabolism. Technical advances in recent years enable us to calculate absolute molar concentrations of metabolites from localized volumes of interest (VOIs) in the brain.[23,24]

STUDY 1

This initial study compared a group of HIV-infected men with varying degrees of HIV-related neuropsychiatric impairment with a control group studied previously as part of an effort to determine normal brain metabolite values. All participants gave informed consent after the nature of the study had been fully explained.

Subjects and Methods

Subjects.—The HIV-infected sample consisted of 17 white homosexual men, 32 to 57 years of age, from the Veterans Affairs Medical Center Infectious Disease Clinic, San Francisco, Calif. Seven patients met the criteria for AIDS of the Centers for Disease Control, Atlanta, Ga; eight met the Centers for Disease Control's criteria for ARC; and two patients were HIV seropositive, but asymptomatic. Of the patients with AIDS, four had been diagnosed with *Pneumocystis carinii* pneumonia, two with lymphoma, and one with Kaposi's sarcoma. Patients were excluded from the study if they had a history of recent head injury, seizure disorder, multiple sclerosis, cerebrovascular disease, active opportunistic CNS infection, another known cause for dementia, major psychiatric illness (defined as schizophrenia, major mood disorder, or anxiety disorder), or preexisting organic brain disorder. Two patients were being treated with zidovudine (azidothymidine) alone and 10 patients were being treated with zidovudine plus other antiviral agents such as acyclovir.

The control group consisted of five men and one woman, 29 to 44 years of age, all without a history of recent medical illness, neurological disease, developmental disorder, psychiatric disorder, or substance abuse. No members of the control group belonged to any group at high risk for HIV infection. These subjects had been studied 6 months previously as control subjects in a study of brain tumors.

Assessment of ADC.—All HIV-infected subjects underwent neuropsychological, psychiatric, and neurological examinations. Neuropsychological testing included measurement of orientation, attention, language, spatial construction skills, calculation, reasoning, and memory. Visual motor coordination, motor speed, and grip strength were assessed to appraise perceptual-motor function. All measures were scored using standardized procedures incorporating age and education corrections when such were available for measure. Psychiatric assessment consisted of a structured psychiatric interview, the Brief Psychiatric Rating Scale, Beck Depression Inventory, and the Symptom Checklist-90. The neurological status of each patient was assessed utilizing the AIDS Treatment Evaluation Unit (ATEU) Neuro-AIDS Assessment Form,[25] which provides a more

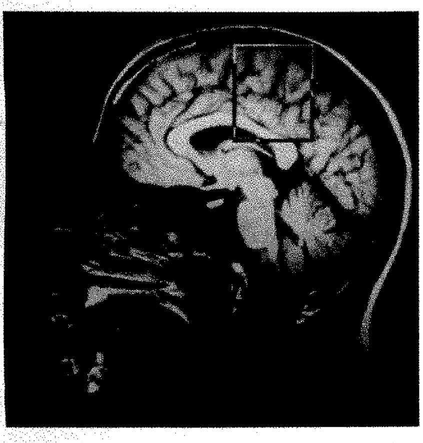

Fig 1.—Sagittal magnetic resonance imaging through the lateral ventricle illustrating the 5 × 5 × 5-cm volume of interest for one of the patients in study 1 who was symptomatic for the human immunodeficiency virus.

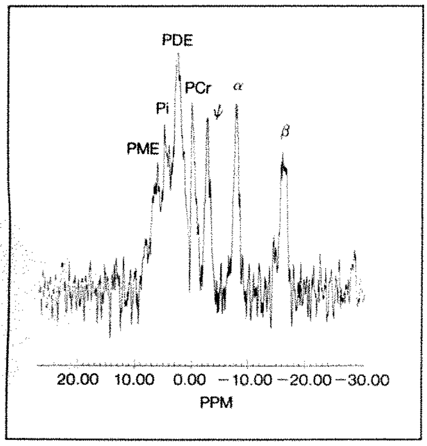

Fig 2.—Illustrative spectrum from the 5 × 5 × 5-cm volume of interest displayed in Fig 1 for a patient who was infected with the human immunodeficiency virus. The letters α, β, and ψ represent the three resonances of adenosine triphosphate, which are averaged to give the concentration of adenosine triphosphate. PME indicates phosphomonoester; Pi, inorganic phosphate; PCr, phosphocreatine; and PDE, phosphodiester.

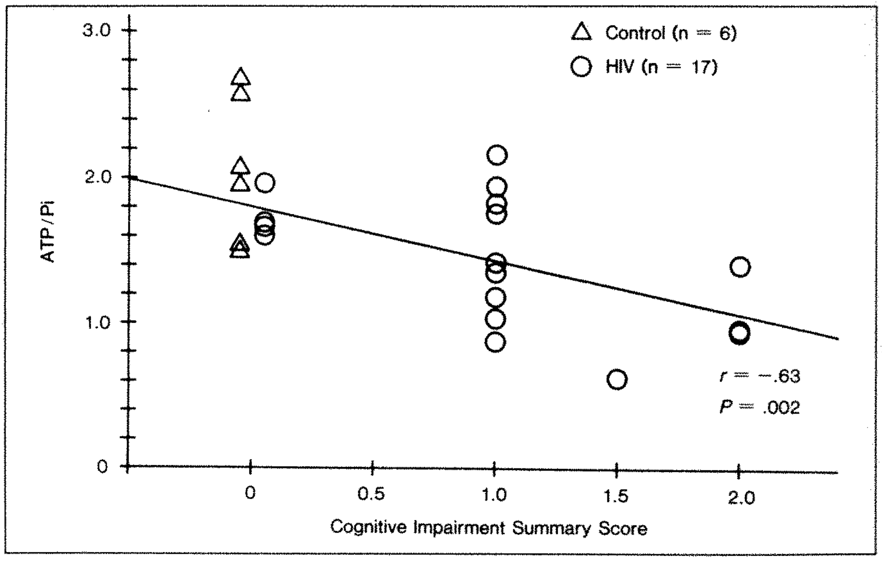

Fig 3.—The ratio of adenosine triphosphate (ATP) to inorganic phosphate (Pi) from the volume of interest vs composite cognitive impairment score is displayed for 17 patients positive for the human immunodeficiency virus (HIV) and six control subjects.

quantitative measure of neurological status than can be obtained from a standard descriptive neurological examination. Utilizing the information obtained from the neuropsychological, psychiatric, and neurological evaluations, each subject was given a summary assessment score for cognitive impairment, behavioral disturbance, and neurological impairment on a four-point scale (0, none; 1, mild; 2, moderate; and 3, severe) utilizing specific parameters established in the ATEU Neuro-AIDS Assessment Form. An overall composite dementia score was then computed for each patient by averaging the cognitive, behavioral, and neurological function summary assessment scores.

MRI and MRS.—All studies were performed in the San Francisco Veterans Affairs Medical Center using a Philips Gyroscan 2.0-T S15 MRI/MRS system. A standard imaging saddle-type proton head coil was used for MRI. For phosphorus 31 MRS, a 16-cm-diameter closely coupled head coil composed of two circular loops was used. Subjects were positioned supine in the magnet with the head inside both coils; the radiofrequency fields of the two coils were orthogonal to each other so that the coils did not interact. A 3-mL external reference of hexamethylphosphorostriamide (HMPT) was positioned in the center of one of the loops of the phosphorus 31 coil. This reference was used (1) to confirm coil position on the magnetic resonance image; (2) to determine the 90° pulse length at the reference position (so that the 90° pulse length at the center of the VOI could be set using a computer-generated B-1 field plot); and (3) as a reference for the relative sensitivity of the loaded coil for the calculation of metabolite concentrations. To accurately select the volume for MRS, T_1 (TR, 600 ms; TE, 30 ms) and T_2 (TR, 2000 ms; TE, 30 and 60 ms)-weighted axial multiple-slice MRIs were obtained. The MRI studies were later blindly rated by a board certified neuroradiologist for any CNS pathologic findings, as well as overall cerebral atrophy, ventricular enlargement, and sulcal enlargement using a four-point rating scale (0, normal; 1, mild; 2, moderate; and 3, severe). The phosphorus 31 coil position was determined through observation of the external standard on the proton image. A 5 × 5 × 5-cm VOI was chosen to coincide with the VOI used in the prior study of brain tumors (which yielded the control data) and is displayed for an illustrative patient study in Fig 1. The magnet was shimmed by observing the proton signal of water (85.9 Hz at 2.0 T) using the proton imaging coil, to a line width of 15 to 25 Hz. The 90° pulse length for phosphorus 31 at the VOI position was determined from the phosphorus 31 signal of the external HMPT reference standard and calculated for the center of the VOI using a computer-generated B-1 field plot. A one-pulse spectrum of the HMPT standard was recorded with a 90° excitation pulse for calibration of the loaded coil sensitivity. Finally, phosphorus 31 spectra were acquired using the improved image-selected in vivo spectroscopy (ISIS) method[26] at 2.0 T. Acquisition parameters were as follows: repetition time, 2 seconds; sweep width, 2 kHz; number of scans, 640; and data size, 1000.

Phosphorus 31 data were processed using the NMR-1 program on a Sun Systems workstation. The broad signal from the less-mobile metabolites was removed by convolution difference and baseline flattening procedures. In addition, an exponential line-broadening factor of 5 Hz was used. Integrals from individual resonance signals were then obtained from least-squares curve-fitted spectra and used for calculation of concentrations[24] and ratios of peak integrals with correction for T_1 saturation.[27] The correction for T_1 saturation is especially important for PCr, for which the pulse repetition time (TR) is less than 2 T_1. For calculation of brain metabolite concentrations in millimoles per liter, an 80% water content was assumed. The metabolites assessed included ATP, Pi, PCr, PME, and PDE. A sample spectrum from a patient with HIV is shown in Fig 2.

pH Measurement.—The pH was calculated from the chemical shift of inorganic phosphate (δPi) referenced to the chemical shift of phosphocreatine (δPCr), which was assumed to be 0 ppm, where δPi and δPCr were obtained from the curve-fitted peak positions:

$$pH = 6.77 + \log(\delta \mathrm{Pi} - 3.29)/(5.68 - \delta \mathrm{Pi})$$

Results

Data were initially analyzed to determine if the 17 HIV-infected patients had different concentrations of high-energy phosphates compared with the normal control subjects. The ATP/Pi ratio in brain was lower for the HIV patients compared with the normal control subjects (1.45 ± 0.45 vs 2.07 ± 0.50, $P = .03$). The absolute magnitude of the difference between groups was the same for the PCr/Pi ratio, but the variance of the ratios was somewhat larger (2.32 ± 0.77 vs 2.96 ± 0.83, $P = .10$). These comparisons were unchanged when examined using nonparametric statistics. These differences between the samples were due to lower ATP and PCr concentrations and slightly higher Pi concentrations in the HIV group, although, because of relatively large between-subject variance of absolute concentrations, none of the absolute concentrations significantly differentiated the samples. There were no significant differences between patients with HIV and control subjects concerning PME or PDE concentrations or the ratios involving these measures.

MRS and Composite Dementia Scores.—When the high-energy phosphates of both the controls and patients with HIV were examined in relationship with the neuropsychiatric summary assessment scores, a number of significant correlations resulted. The ATP/Pi ratio had a significant negative correlation with each of the summary assessment scores ($r = -0.63$, $P = .002$; $r = -.44$, $P = .04$; $r = -.46$, $P = .03$; and $r = -.057$, $P = .005$ for the cognitive, neurological, behavioral, and composite dementia scores, respectively). A scatterplot of the ATP/Pi ratios vs the cognitive impairment summary score is displayed in Fig 3. Comparable significant negative correlations were noted between the PCr/Pi ratios and the summary assessment scores ($r = -.45$, $P = .03$; $r = -.24$, $P = .28$; $r = -.53$, $P = .01$; and $r = -.047$, $P = .03$ for the cognitive, neurological, behavioral, and composite dementia scores, respectively). There were no significant correlations between any of the phospholipid metabolite measures and any of the composite dementia scores.

MRS and Illness Severity.—There were no significant group differences in ATP/Pi or PCr/Pi ratios for patients with AIDS vs patients with ARC. In addition, of nine patients who had CD4 lymphocyte measurements obtained at the time of the study, there were no significant correlations between ATP/Pi or PCr/Pi ratios and absolute CD4 lymphocyte counts. Weight loss was also examined in relation to the ATP/Pi ratio. Three patients had a weight loss of 2.25 kg (5 lb) or greater in the 6 months before enrolling in the study. The ATP/Pi ratio for these patients was 1.51 ± 0.62, which was not significantly different from the corresponding values for the entire ADC group (1.45 ± 0.45).

Cerebral Atrophy.—Eleven of 17 HIV-infected patients had full T_1-weighted MRI studies that were evaluated for evidence of cerebral atrophy and other CNS pathology. Five patients had evidence of atrophy, and no other abnormalities were noted. Measurements of cerebral atrophy were not significantly correlated with the ATP/Pi and PCr/Pi ratios or ATP or PCr concentrations. However, ventricular enlargement was positively correlated with pH ($r = .78$, $P = .007$) and negatively correlated with the PME concentration ($r = -.63$, $P = .038$). Sulcal enlargement scores were positively correlated with the cognitive disturbance summary scores ($r = .66$, $P = .03$).

COMMENT

Although preliminary, the results of study 1 suggest a decrease in brain oxidative metabolism in patients with HIV infection, with the magnitude of the effect directly associated with the magnitude of the patient's neuropsychiatric impairment.

We do not believe that the MRS changes are the result of more cerebrospinal fluid in the brain VOIs of patients with neuropsychiatric impairment because (1) measurements of cerebral atrophy were not significantly correlated with the ATP/Pi or PCr/Pi ratios or ATP concentration; (2) MRS studies of dementias in the elderly do not report decreased ATP/Pi ratios in the presence of cortical atrophy[28]; (3) our examination of two sagittal images through the lateral ventricles in 10 patients in study 1 (the five with the highest and lowest ATP/Pi ratios did not reveal any correlation between the total ventricular and sulcal area within the MRS VOI and the ATP/Pi ratios); and (4) the concentration of Pi in cerebrospinal fluid (0.17 mol/L)[29] is an order of magnitude smaller than the concentration in brain, and the concentration of ATP in cerebrospinal fluid is even smaller; thus, the effect of relatively small differences in the proportion of cerebrospinal fluid in the MRS volume should be to decrease the absolute concentrations, with little, if any, effect on ratios. Finally, although the quantitation of metabolite concentrations requires assumptions regarding the tissue water content, and it is possible that tissue water content differs between groups, such differences would have to affect concentrations of all metabolites equally and could not underlie the specific changes we observed in ATP and PCr concentrations.

Because the 5 × 5 × 5-cm VOI is a heterogeneous volume containing substantial contributions from white matter, gray matter, and ventricular cerebrospinal fluid, and because the weight of histological and neuroimaging studies indicates preferential subcortical involvement by HIV in the CNS, we refined our MRS procedures for study 2 to determine whether the MRS changes are specific to white matter or subcortical gray matter. In addition, preliminary data from our laboratory suggest that phosphorus metabolite concentrations are strongly affected by varying the brain region studied.[30] Thus, we believed that studying more homogeneous VOIs would yield less variable concentration measures across subjects within each group, increasing the statistical power of group comparisons. For study 2, we also selected a more appropriate control group, age and sex matched to the patients with HIV, but with documented HIV seronegativity.

STUDY 2

Subjects and Methods

Subjects.—In the second part of our ongoing study, we have, so far, studied 12 heterosexual male control subjects (mean age ± SD, 24.8 ± 4.4 years) in whom HIV seronegativity was confirmed by HIV-antibody testing (enzyme-linked immunosorbent assay) and three HIV-infected patients with moderate-to-severe neuropsychiatric impairments. All control subjects were examined and found to be cognitively unimpaired using the same neuropsychological battery as used in the examination of the HIV-infected patients. Inclusion and exclusion criteria were as described for study 1 subjects. All three HIV-infected patients carried a diagnosis of ARC, and two patients were receiving zidovudine at the time of study.

MRI and MRS.—Procedures were identical to those described in study 1, except that we selected two different VOIs to better characterize metabolic alterations in subcortical gray matter and white matter. The subcortical gray matter VOI (Fig 4) encompassed the insulae, claustrum, putamen, caudate, globus pallidus, and thalamus bilaterally with minimal white matter contamination. The white matter VOI (Fig 4) encompassed the centra semiovale bilaterally, bordered inferiorly by the inferior margin of the corpus callosum and laterally and superiorly by the inner margin of the cortical mantle. For calculation of brain metabolite concentrations in millimoles per liter, a 72% water content was assumed for the white matter VOI, and an 82% water content was assumed for the gray matter VOI.

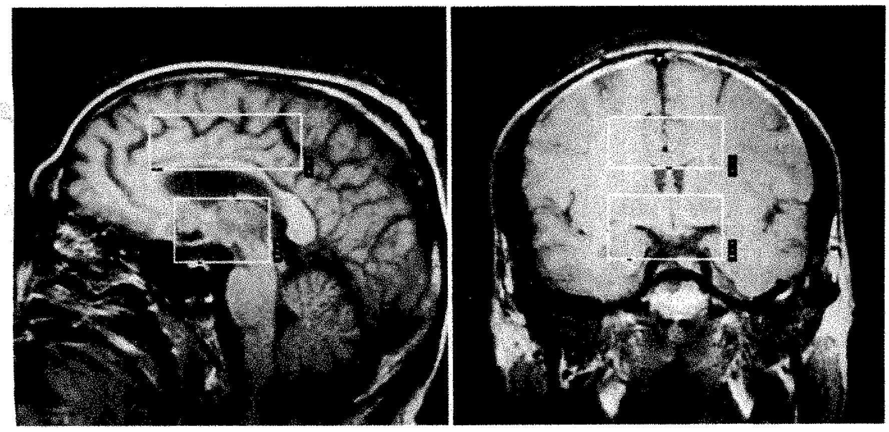

Fig 4.—These two magnetic resonance images illustrate the white matter (outlined in white) and subcortical gray matter (outlined in black) volumes of interest from study 2.

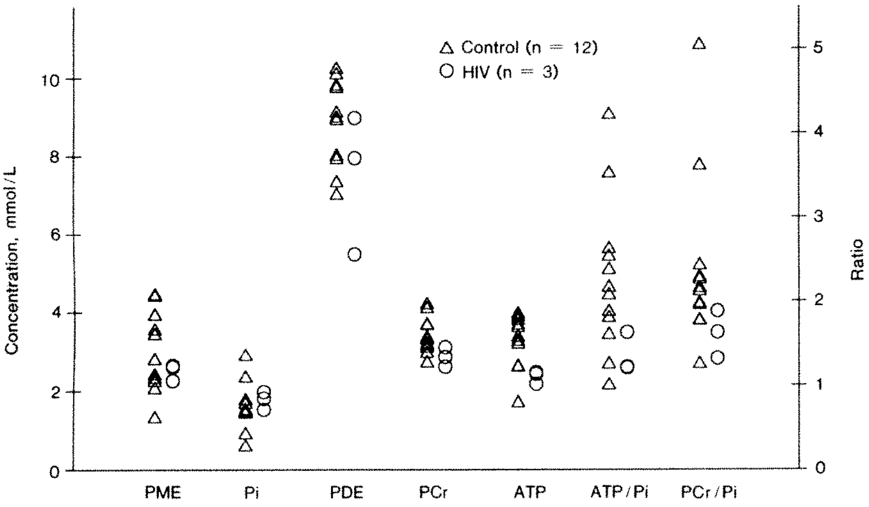

Fig 5.—Phosphorus 31 metabolic concentrations for the white matter volume of interest in Fig 4. PME indicates phosphomonoester; Pi, inorganic phosphate; PDE, phosphodiester; PCr, phosphocreatine; ATP, adenosine triphosphate; and HIV, human immunodeficiency virus.

Results

For the white matter VOI, the HIV-infected patients evidenced decreased ATP and PCr concentrations ($P = .036$ for both, Mann-Whitney *U* test) and trends for decreased ATP/Pi ratios and PCr/Pi ratios ($P = .073$ for both, Mann-Whitney *U* test). Metabolite concentrations and ratios are displayed in Fig 5. For the subcortical gray matter VOI, no differences between the ADC and control groups were apparent on any variables. The SEs of the absolute metabolite concentrations were smaller (about 5% to 7% of the mean value) than were the SEs from the 5 × 5 × 5-cm VOI in study 1.

COMMENT

These preliminary studies strongly suggest that patients with neuropsychiatric impairment secondary to HIV infection of the brain may have impaired brain cellular oxidative metabolism. In study 1, we found that, compared with control subjects, patients with HIV-related neuropsychiatric impairment had significantly reduced brain ATP/Pi ratios and a trend for reduced brain PCr/Pi ratios, with the reduced ratios primarily reflecting reduced ATP and PCr concentrations. These findings are in agreement with the abstract by Bottomley et al[21] that reported significant reductions in ATP and PCr concentrations in eight patients with ADC compared with control subjects. Although our PCr/Pi ratios are higher than those generally reported in the literature, this is because we correct for T_1 saturation. Without the T_1 saturation correction, our PCr/Pi ratio for the control subjects in study 1 is 1.89 ± 0.56, which is in close agreement with that reported by others.[30-32] The correction is important because the long T_1 values for PCr will yield markedly different results if different repetition times are used in various laboratories.

Because of the heterogeneous nature of the study 1 VOIs and evidence from our laboratory that phosphorus metabolite concentrations vary considerably across different brain regions,[33] we selected more homogeneous VOIs for study 2. In study 2, we examined primarily white matter and primarily subcortical gray matter VOIs. Although we studied only three patients for the white matter VOI and two patients for the subcortical gray matter VOI, the decrease in ATP and PCr concentrations appeared to be specific to the white matter VOIs. Although this very preliminary result clearly requires confirmation with a larger sample size, it is in agreement with neurohistological and MRI data revealing major HIV-related neuropathology in white matter.[1,15,16]

The results from study 1 also suggest that the degree of metabolic compromise may be related to the severity of neuropsychiatric impairment, as evidenced by significant negative correlations between the ATP/Pi and PCr/Pi ratios and the neuropsychiatric summary assessment scores. This is the first in vivo MRS study, to our knowledge, to report an association between the severity of HIV-related neuropsychiatric impairment and the degree of impaired brain energy metabolism. This finding is consistent with the results of Pohl et al,[20] who noted that worsening of dementia in patients with ADC was associated with an increase in uptake defects (decreased local cerebral blood flow and disturbed cerebral amine metabolism) on single-photon emission computed tomography. If this association is corroborated by further study, in vivo phosphorus 31 MRS may hold promise for monitoring biological factors associated with HIV disease progression in the brain and for monitoring response to treatment with medications that improve HIV-related neuropsychiatric impairment, such as zidovudine.[34,35]

The association of HIV-related neuropsychiatric impairment with changes in brain high-energy phosphorus metabolism suggests two nonexclusive possibilities. The first is that the metabolic alterations are due to a severe metabolic disturbance in focal areas with the VOI. The second possibility is that the metabolic alterations are due to a process that affects most or all cells within the VOI. To determine if the nature and extent of HIV-related MRS-determined metabolic alterations are due to focal lesions, we are currently attempting to correlate MRI findings (brain atrophy and white-matter disease) with MRS results. If we find that MRS detected changes that occurred in VOIs with absent or very few focal MRI lesions, this will be interpreted to suggest that the metabolic changes are due to a process that affects most cells with the VOI.

It is unclear at this time whether altered brain phosphorus metabolism is specific to HIV disease or is a general finding reflective of a progressive subcortical dementing process. There have been very few in vivo phosphorus 31 MRS studies of subcortical dementia syndromes such as Parkinson's or Huntington's dementia. One small study of Parkinson's disease[28] found no significant differences in the ratios of cerebral phosphate metabolites such as PCr/Pi compared with control subjects. Nevertheless, it is conceivable that our findings of impaired energy metabolism could be the consequence of the subcortical nature of HIV-related neuropsychiatric impairment and would be present in other subcortical dementia syndromes as well. Therefore, we are currently undertaking in vivo phosphorus 31 MRS studies of non-HIV-related subcortical dementias (such as multiple sclerosis-related dementia) to address this issue. In vitro and in vivo phosphorus 31 MRS studies of cortical dementias such as Alzheimer's and multi-infarct dementia have revealed alterations primarily in the PME and PDE resonances with no significant changes in measurements or indexes of cellular oxidative metabolism.[28,36-39]

Our ongoing in vivo phosphorus 31 MRS study of deep white-matter lesions (also called leuko-araiosis) in demented and nondemented elderly subjects also provides interesting comparative data. In white matter VOIs, we have found significant reductions in the ATP/Pi ratios and PDE concentration associated with the presence of extensive deep white-matter lesions, but unrelated to the presence of dementia.[40] In the current study, where many of the HIV-infected patients also have white-matter lesions evidenced on MRI, we find a similar decrease in the ATP/Pi ratio but fail to find a decrease in the PDE concentration. This may indicate that the mechanisms underlying the white-matter changes differ in the two disease processes or may reflect a difference in the severity of disease in the two cases.

This study illustrates the importance of quantitation methodology, along with image-guided three-dimensional localized phosphorus 31 MRS. We used an improved ISIS technique[26] to obtain MRI-localized phosphorus 31 MRS of human brain. This technique, which has been carefully studied in computer-simulated analyses and phantom studies,[24] provides accurate localization for characterization of relatively homogeneous human brain VOIs.

There are a number of simplifying assumptions that, as we have noted previously,[24] are involved in the calculation of molar concentrations. First, for quantitation, the tissue within the VOI is assumed to be homogeneous, with the measured concentrations representing the mean concentration within the VOI. Second, the T_1 values used to calculate concentrations were derived from normal subjects for large brain volumes, which were less homogeneous than the VOIs of the current study. This was necessary because of the tremendously lengthy study times necessary to measure phosphorus 31 T_1 values. We estimated that a T_1 study for each metabolite separately for the white matter and subcortical gray matter VOIs would involve having each subject spend several hours in the magnet for each VOI. Third, our measurements could be influenced by variation between subjects in metabolite mobility as well as in metabolite concentration. Fourth, we assumed a uniform tissue water content for each VOI across subjects. If the water content varied among subjects, that could have affected the concentrations, but it would have affected all metabolites equally.

The simplifying assumptions noted above argue for caution in the interpretation of our results. The results clearly indicate that there are changes in aspects of the phosphorus 31 MRS associated with HIV infection. Although it is possible that the effect reflects differential changes in the mobility of the various metabolites, or in their T_1 values, we do not believe it is likely. Our preliminary simulations suggest that the effect of differences between metabolites in mobility and T_1 values would be small compared with the effect of differences in metabolite concentration (except possibly for PCr, where the T_1 time is greater than the repetition time). Thus, the most parsimonious interpretation of our results is that they reflect concentration differences.

Finally, it is important to note that the in vivo phosphorus 31 MRS technique is in its infancy. We fully expect great advances in magnet strength, pulsing technology, and phosphorus 31 spectroscopic imaging. These advances will result in the ability to quantitate metabolite concentrations throughout the brain in ever smaller voxels. Such advances, together with the development of proton MRS technology, portend an explosion of in vivo studies of brain metabolism in normal and pathological conditions.

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References

1. Navia BA, Jordan BD, Price RW. The AIDS dementia complex, I: clinical features. *Ann Neurol.* 1986;19:517-524.

2. Navia BA, Price RW. Central and peripheral nervous system complications of AIDS. *Clin Immunol Allergy.* 1986;124:537-558.

3. Price RW, Breu B, Sidtis J, Rosenblum M, Scheck AC, Cleary P. The brain in AIDS: central nervous system HIV-1 infection and AIDS dementia complex. *Science.* 1988;239:586-592.

4. Snider WD, Simpson DM, Nielsen S, Gold JWM, Metroka CE, Posner JB. Neurological complications of acquired immune deficiency syndrome: analysis of 50 patients. *Ann Neurol.* 1983; 14:403-418.

5. Anders KH, Guerra WF, Tomiyasu U, Verity MA, Vinters HV. The neuropathology of AIDS: UCLA experience and review. *Am J Pathol.* 1986; 124:537-558.

6. Levy RM, Bredesen DE, Rosenblum ML. Neurological manifestations of AIDS: experience and review of the literature. *Neurosurgery.* 1985; 62:475-495.

7. Detmer W, Lu FG. Neuropsychiatric complications of AIDS: a literature review. *Int J Psychiatry Med.* 1986;16:21-29.

8. Pumalrola-Sune T, Navia BA, Cordon-Cardo C, Cho E-S, Price RW. HIV antigen in the brains of patients with the AIDS dementia complex. *Ann Neurol.* 1987;21:490-496.

9. Gabuzda DH, Ho DD, de la Monte SM, Hirsch MS, Rota TR, Sobel RA. Immunohistochemical identification of HTLV-III antigen in brains of patients with AIDS. *Ann Neurol.* 1986;20:289-295.

10. Wiley CA, Schrier RD, Nelson JA, Lampert PW, Oldstone MBA. Cellular localization of human immunodeficiency virus infection within the brains of acquired immune deficiency syndrome patients. *Proc Natl Acad Sci U S A.* 1986;83:7089-7093.

11. Koenig S, Gendelman HE, Orenstein JM, et al. Detection of AIDS virus in macrophages in brain tissue from AIDS patients with encephalopathy. *Science.* 1986;233:1089-1093.

12. Epstein LG, Goudsmit J, Paul DA, et al. Expression of human immunodeficiency virus in cerebrospinal fluid of children with progressive encephalopathy. *Ann Neurol.* 1987;21:397-401.

13. Ho DD, Rota TR, Schooley RT, et al. Isolation of HTLV-III from cerebrospinal fluid and neural tissues of patients with neurologic syndromes related to the acquired immunodeficiency syndrome. *N Engl J Med.* 1985;313:1494-1497.

14. Rottenberg DA, Moeller JR, Strother SC, et al. The metabolic pathology of the AIDS dementia complex. *Ann Neurol.* 1987;22:700-706.

15. Donovan Post MJ, Sheldon JJ, Hensley GT, et al. Central nervous system disease in acquired

immunodeficiency syndrome: prospective correlation using CT, MR imaging, and pathologic studies. *Radiology.* 1986;158:141-148.

16. Grant I, Atkinson JH, Hesselink JR, et al. Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus infections. *Ann Intern Med.* 1987; 107:828-836.

17. Cummings JL. Subcortical dementia: neuropsychology, neuropsychiatry, and pathophysiology. *Br J Neurol.* 1986;149:682-697.

18. Brouwers P, Mohn E, Hendricks M, et al. Comparison of HIV to Alzheimer's (AD) and Huntington's (HD) dementias: differential neuropsychological patterns. Program and abstracts of the Fourth International Conference on AIDS; June 12-16, 1988; Stockholm, Sweden. Abstract 7046.

19. Van Gorp WG, Miller EN, Satz P, Visscher B. Neuropsychological performance in HIV-1 immunocompromised patients. *J Clin Exp Neuropsychol.* 1989;5:763-773.

20. Pohl P, Vogl G, Fill H, Rossler H, Zangerle R, Gerstenbrand F. Single photon emission computed tomography in AIDS dementia complex. *J Nucl Med.* 1988;29:1382-1386.

21. Bottomley PA, Hardy CJ, Cousins J, Armstrong M, Wagle W. Brain phosphate metabolite concentrations, not ratios, are reduced in AIDS dementia. *Proc Soc Magnetic Resonance Med.* 1989;1:369.

22. Arnold DL, Bore PJ, Radda GK, Styles P, Taylor DJ. Excessive intracellular acidosis of skeletal muscle on exercise in a patient with a post-viral exhaustion/fatigue syndrome: a ^{31}P nuclear magnetic resonance study. *Lancet.* 1984; 1:1367-1369.

23. Ordidge RJ, Connelly A, Lohman JAB. Image-selected in-vivo spectroscopy (ISIS). *J Magnetic Resonance.* 1986;66:283.

24. Roth K, Hubesch B, Meyerhoff DJ, et al. Noninvasive quantitation of phosphorus metabolites in human tissue by NMR spectroscopy. *J Magnetic Resonance.* 1989;81:299-311.

25. Sidtis JJ, Amitai H, Ornitz D, Price RW. The brief neuropsychological examination for AIDS dementia complex: correlations with functional status scales and other neuropsychological tests. Program and abstracts of the Third International Conference on AIDS; June 1-5, 1987; Washington, DC. Abstract T.5.1.

26. Matson GB, Twieg DB, Karczmar GS, et al. Application of image-guided surface coil ^{31}P MR spectroscopy to human liver, heart, and kidney. *Radiology.* 1988;169:541-547.

27. Hubesch B, Sappey-Marinier D, Roth K, Meyerhoff DJ, Matson GB, Weiner MW. P-31 MR spectroscopy of normal human brain and brain tumors. *Radiology.* 1990;174:401-409.

28. Bueri JA, Gorell JM, Levine SR, et al. Cerebral phosphate metabolism in Alzheimer and Parkinson dementia measured by ^{31}P NMR spectroscopy. *Neurology.* 1987;37(suppl 1):160.

29. Siegel GJ, Agranoff BW, Albers RW, Molinoff P, eds. *Basic Neurochemistry: Molecular, Cellular, and Medical Aspects.* 4th ed. New York, NY: Raven Press; 1989.

30. Welch KMA, Levine SR, D'Andrea G, Schultz LR, Helpern JA. Preliminary observations on brain energy metabolism in migraine studied by in vivo phosphorus 31 NMR spectroscopy. *Neurology.* 1989;39:538-541.

31. Brown GG, Levine SR, Gorell JM, et al. In vivo ^{31}P NMR profiles of Alzheimer's disease and multiple subcortical infarct dementia. *Neurology.* 1989;39:1423-1427.

32. Arnold DL, Shoubridge EA, Feindel W, Villemure JG. Metabolic changes in cerebral gliomas within hours of treatment with intra-arterial BCNU demonstrated by phosphorus magnetic resonance spectroscopy. *Can J Neurol Sci.* 1987; 14:570-575.

33. Hubesch B, Sappey-Marinier D, Deicken R, Seidenwurm D, Weiner MW. Regional differences of phosphorus metabolites in the human brain. *Proc Soc Magnetic Resonance Med.* 1989;1:447.

34. Schmitt FA, Bigley JW, McKinnis R, et al. Neuropsychological outcome of zidovudine (AZT) treatment of patients with AIDS and AIDS-related complex. *N Engl J Med.* 1988;319:1573-1578.

35. Yarchoan R, Berg G, Brouwers P, et al. Response of human-immunodeficiency virus-associated neurological disease to 3′-azido-3′-deoxythymidine. *Lancet.* 1987;1:132-135.

36. Miatto O, Gonzales RG, Buonanno F, Growdon JH. In-vitro ^{31}P NMR spectroscopy detects altered phospholipid metabolism in Alzheimer's disease. *Neuropathol Exp Neurol.* 1988;47:235-248.

37. Levine SR, Welch KMA, Helpern JA, Ewing JR, Bruce R, Smith MB. ^{31}P NMR spectroscopy study of multi-infarct dementia. *Neurology.* 1987; 37(suppl 1):251.

38. Pettegrew JW, Moossy J, Withers G, McKeag D, Panchalingam K. ^{31}P nuclear magnetic resonance study of the brain in Alzheimer's disease. *J Neuropathol Exp Neurol.* 1988;47:235-248.

39. Smith CD, Gallenstein LG, Markesbery WR. ^{31}P spectroscopy in Alzheimer's and Pick's disease using post-mortem perchloric acid brain extracts. *Proc Soc Magnetic Resonance Med.* 1988;1:444.

40. Sappey-Marinier D, Hubesch B, Deicken R, Fein G, Matson GB, Weiner MW. Altered phosphate concentrations and pH in patients with chronic stroke and DWMLs. *Proc Soc Magnetic Resonance Med.* 1989;3:1070.

The Effect of Sleep on the Dyskinetic Movements of Parkinson's Disease, Gilles de la Tourette Syndrome, Huntington's Disease, and Torsion Dystonia

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• The effect of sleep on the involuntary movements or dyskinesias in Parkinson's disease, Huntington's disease, primary and secondary torsion dystonia, and Gilles de la Tourette syndrome was studied in a total of 52 patients and 10 normal subjects using video electroencephalographic telemetry. Movements typical of the wake pattern were seen occasionally during unequivocal sleep in all but two completed studies, and in each condition reappeared under similar circumstances. The movements were most likely to occur after awakenings or lightenings of sleep, or in stage one sleep. The movements were very rare during the deeper phases of sleep. Those movements that occurred during sleep without awakenings were usually preceded by arousal phenomena and, rarely, by sleep spindles or slow waves. The control group showed normal "semipurposeful" movements under the same conditions during sleep. The rare appearance of the different dyskinesias and normal movements under similar circumstances during sleep could be a result of common effects on the generator systems or changes in the excitability of the final common motor pathway.

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The widely held belief that most involuntary movements or dyskinesias, except for certain types of myoclonus, cease completely during sleep[1-3] has been shown to be incorrect.[4,5] However, the exact circumstances during sleep under which occasional movements may reappear have not been defined. Unfortunately, previous studies have used inappropriate methods of sleep staging, failed to identify the precise electroencephalographic (EEG) phenomena associated with each movement, or have not characterized the movements themselves.

For the purposes of sleep staging, the overnight record is usually divided into fixed epochs of 20 or 30 seconds.[6] Most epochs contain a mixture of sleep phenomena that may be used to classify each epoch as stages one to four or rapid eye movement (REM) sleep according to the criteria of Rechtschaffen and Kales.[6] However, the fixed-time base employed in this assessment leads to transition epochs that really contain sleep of two different stages. For example, Fig 1 shows a transition from stage two to wake. The first half of the epoch contains sleep phenomena with a low-amplitude submental electromyogram (EMG), background theta activity, and a K complex. Just into the second half of the epoch, alpha rhythm develops. This is followed by a head movement artifact and an increase in submental tone. Conventionally such epochs are scored according to the type of sleep occupying the majority of the period,[6] which, in this case, would be stage two sleep. This approximation has little effect on the overall description of the sleep pattern because transition epochs account for only 3% to 6% of the normal overnight record.[7] However, events that occur in association with changes in sleep stage could be designated inappropriately. Earlier reports[4,8,9] suggest that arousal phenomena frequently precede nocturnal movements. Therefore, studies relying solely on scoring systems such as that described by Rechtschaffen and Kales[6] may be misleading.

The precise EEG phenomena associated with each movement are important because arousals may occur that are insufficient to cause a change in sleep stage,[10] and motor function may vary with specific EEG phenomena. For example, in animals there is a marked reduction in the frequency of spontaneous motor unit discharges in association with sleep spindles,[11] and intracellular recordings in cats have shown rapid changes in the membrane potential of alpha motor neurons during REMs.[12]

Involuntary movements may be identified using surface EMG, but such recordings alone may not distinguish different types of movement. Visual confirmation is often necessary to determine the nature of sleep movements.

In 1964 and 1965, Tassinari et al[4,13] reported the effect of sleep on involuntary movements in several groups of movement disorders. Qualitative direct observations combined with EEG

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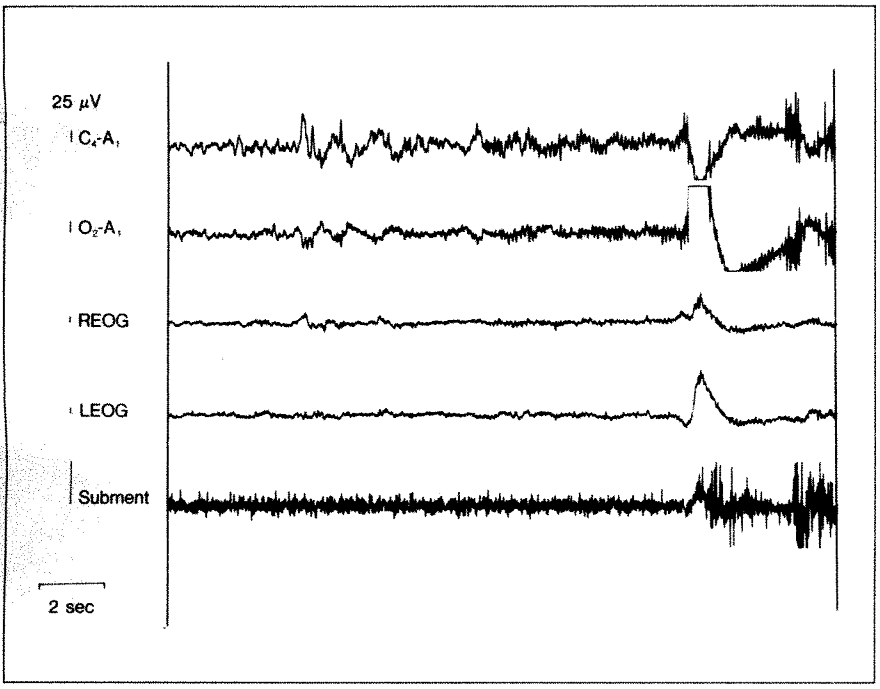

Fig 1.—A 20-second fixed epoch showing a transition from sleep to wakefulness. REOG indicates right electro-oculogram; LEOG, left electro-oculogram; SM, submentalis surface electromyogram.

Table 1.—The Number of Patients in Each Group

Group	No. of Subjects
Normal subjects	10
Parkinson's disease	10
Huntington's disease	5
Gilles de la Tourette syndrome	13
Primary generalized torsion dystonia	14
Secondary torsion dystonia	10
Total	**62**

and EMG recordings suggested that most movements decreased or stopped on falling asleep, but both parkinsonian tremor and "nonrhythmic movements (such as choreic syndromes)" were observed occasionally during all sleep stages, usually in association with awakenings, lightening of sleep, and global or segmental body movements. However, the precise EEG phenomena preceding each type of movement were not described. Subsequently, Mano et al[5] attempted to quantitate the overnight activity of patients with dyskinesias. In four patients with choreoathetosis, one patient with ballismus, and four patients with secondary dystonia, the frequency of "characteristic surface EMG discharges" showed a reduction from wake through stages one to four with stage REM giving a level similar to that of stage one or two sleep.

The findings of Tassinari et al[4,13] and Mano et al[5] have been supplemented by investigations that have been limited to a single-movement disorder, although methodological differences impair direct comparisons. Parkinsonian tremor has been extensively studied during sleep, but the results have been conflicting. Parkinson himself observed that tremor could occur during sleep in advanced cases of the shaking palsy,[14] and this was supported by Gowers,[15] but both Froment and Delore[16] and Friedlander[17] failed to observe tremor during sleep in such patients. Accelerometer recordings, however, confirmed the occurrence of tremor during sleep in Parkinson's disease, particularly in association with awakenings or body movements, and showed brief bursts of tremor during stage REM sleep.[8,9] The occurrence of parkinsonian tremor during non-REM sleep in the absence of behavioral or EEG evidence of arousal has also been reported,[8] although not confirmed by Stern et al[9] who noted the appearance of posterior alpha rhythm prior to episodes of tremor during epochs of sleep that were scored as stage two. The amplitude of tremor during sleep was observed to be half to two thirds that of wake,[9] and to show marked beat-to-beat variation (particularly in stage REM sleep), although the frequency was unchanged.[8,9] With regard to dystonia, brief bursts of asymmetrical sternocleidomastoid surface EMG activity were recorded during stage REM sleep in eight of 16 patients with spasmodic torticollis.[18] In Gilles de la Tourette syndrome surface EMG, accelerometer, and video recordings demonstrated tics during all sleep stages in 10 children or young adults.[19] The mean number of tics per night during sleep was only 12, and the proportion of tics occurring in each sleep stage was not determined. No tics were recorded during sleep in two older subjects (aged 37 and 48 years) with this syndrome.

The present study investigated the effect of sleep on the expression of parkinsonian tremor, Huntington's disease, Gilles de la Tourette syndrome, primary and secondary torsion dystonia, and "semipurposeful" global or gestural movements in normal subjects.

SUBJECTS AND METHODS

Subjects

Sixty-two subjects were studied (Table 1) with the approval of the Medical Ethics Committee of The National Hospital for Neurology and Neurosurgery Diseases, London, England. No alterations were made to treatment, and all subjects gave informed consent. Thirty-seven of the patients were taking medication. These included 14 patients who were taking benzodiazepines, 15 who were taking anticholinergics, 11 who were taking dopaminergic drugs, and 10 who were taking antidopaminergic drugs. One patient with Parkinson's disease had previously undergone a unilateral thalamotomy (ipsilateral to the limb studied), and two patients with primary torsion dystonia had had bilateral thalamotomies.

Methods

Sleep studies were performed in a quiet single room after one night of adaptation using the split-screen video cable EEG telemetry equipment described by Roberts and Fitch.[20] This provided up to nine channels of electrophysiological monitoring in addition to the time code. Six channels were used to record sleep following the recommendations of Rechtschaffen and Kales,[6] and up to three were used to record movements. Movements were monitored using surface EMG pad electrodes 1.5 cm in diameter or accelerometer (Siemens type 230) recordings from appropriate muscle groups, and a low light-intensity video camera. The paper records were coded and scored blind to the clinical information by one of us (D.R.F.) using the recommendations of Rechtschaffen and Kales[6] with the following amendments to describe transition epochs: lightening (L), an epoch that contained a transition from a deeper stage to a lighter stage of sleep; awakening (A), an epoch that contained a transition from sleep to wake; deepening (D), an epoch that contained a transition from a lighter stage to a deeper stage of sleep; and predormitory (P), an epoch that contained a transition

Table 2.—The Number of Movements per Night During Sleep in Each Group

Group	No. of Completed Studies	No. of Characteristic Movements		
		Total	Median	Range
Normal subjects*	8	251	31.5	26-57
Parkinson's disease	10	132	12	1-61
Huntington's disease	5	204	15	13-107
Primary dystonia	12	203	8.5	1-54
Secondary dystonia	6	213	11.5	5-114
Gilles de la Tourette syndrome	10	143	11.5	0-57

*Normal subjects often made normal "semipurposeful" movements during sleep.

Table 3.—The Median Number of Epochs Containing a Movement per 100 Epochs of the Sleep Stage for Semipurposeful Movements and Nonmyoclonic Movement Disorders*

Group	Sleep Stage					
	W	A	L	1	2	R
Normal	. . .	60	42	8.1	2.3	1.6
Parkinson's disease	16	13	5.4	2.6	0.5	1.9
Huntington's disease	88	67	33	6.4	1.6	0.9
Primary dystonia	40	27	22	3.7	0.3	0
Secondary dystonia	95	32	28	7.1	0.2	0
Gilles de la Tourette syndrome	43	32	14	1.9	0.5	0

*W indicates wake; A, awakening; L, lightening; 1 and 2, stages 1 and 2 sleep; and REM, stage rapid eye movement sleep.

Table 4.—The Timing of Movements During Awakening (A) and Lightening (L) in Relation to the Onset of the Change in Sleep Stage

Group	Movements in Stage A or L	
	No.	Proportion After the Shift in Electroencephalogram*
Normal	89	0.89†
Parkinson's disease	69	0.93†
Huntington's disease	62	0.83†
Primary dystonia	76	0.97†
Secondary dystonia	60	0.83†
Gilles de la Tourette syndrome	63	0.73‡

*Chance = 0.5.
†$P < .0001$, two-tailed binomial statistics.
‡$P < .001$, two-tailed binomial statistics.

Table 5.—The Specific Electroencephalographic Events Before Movements

Group	Relative Risk of Specific Electroencephalographic Event in the Preceding Miniepoch*			
	Arousal	Rapid Eye Movement	Sleep Spindle	Slow Wave
Normal	5.8†	0.76	0.08†	0†
Parkinson's disease	5.1†	3.2†‡	0	0†
Huntington's disease	4.8†	1.5	0.06†	0†
Primary dystonia	3.8†	1.2	0.06	0.15§
Secondary dystonia	4.2†	0.15	0.11†	0.37
Gilles de la Tourette syndrome	3.3†	1.3	0.6	0.17§

*Chance = 1.
†$P < .0001$, χ^2 two-tailed test.
‡Most of this ratio was contributed by one patient with severe Parkinson's disease who had had a previous thalamotomy.
§$P < .01$, χ^2 two-tailed test.

from wake to sleep.

The entire split-screen video recording displaying the neurophysiological data and simultaneous clinical events was reviewed in all cases, and the times of all definite movements were noted. Epochs of awakening or lightening that included a movement were reexamined without reference to the video or movement detector channels in order to determine whether the change in sleep stage preceded or followed the movement.

The onset of each movement that occurred during unequivocal sleep was marked on the paper record after it had been ascribed to a sleep stage. Two randomly timed control marks were then made on the paper record for each movement.

The two-second "miniepoch" prior to each mark was subsequently analyzed blind to the movement channels or video recording for the following phenomena: (1) arousal phenomena: (*a*) increased submental tone above 50% of the baseline and increase in EEG frequency, or (*b*) alpha band rhythm lasting for more than 0.5 second (outside stage REM sleep unless associated with other evidence of arousal), or (*c*) K complex; (2) sleep spindles (11.5 to 15 Hz activity for at least 0.5 second); (3) slow waves (greater than 75 μV peak-to-peak amplitude); and (4) REMs.

This miniepoch length was the shortest needed to readily detect all of the above phenomena. Furthermore, a study of sleep spindles and muscle discharges in rats showed a disparity of up to 1.5 seconds between the onset of a sleep spindle and associated changes in muscle activity.[11] If two or more phenomena occurred together (which happened in less than 5% of events) only the one occupying most of the miniepoch was counted.

The relative risk of a specific EEG phenomena preceding a particular movement was defined as

$$\frac{\text{Percent Premovement Miniepochs Containing the Phenomena}}{\text{Percent Control Miniepochs Containing the Phenomena}}$$

Two hundred eighty-three miniepochs from four randomly selected records were scored by two observers independently (D.R.F. and D.S.) with interobserver and intraobserver repeatabilities of 0.90 and 0.96, respectively.

RESULTS

The Number of Movements During Unequivocal Sleep

Nine patient and two control studies were abandoned because of an inadequate video or neurophysiological record. Movements typical of the wake dyskinesia were documented during unequivocal sleep in 41 of 43 completed studies (Table 2). Control subjects often made apparently normal semipurposeful movements during sleep.

The Reappearance of Movements in Relation to Sleep Stage

Normal Semipurposeful Movements in Control Subjects.—These movements were most frequent during awakenings or lightenings of sleep, and then stage one sleep. They were rare during stages two and REM (Table 3), and virtually absent during stages three, four, predormitory, and deepening (median scores zero in all four of these categories). The voluntary control of such movements precluded a meaningful assessment of the frequency during wakefulness.

Dyskinesias in Patients With Movement Disorders.—The number of epochs that contained a movement per 100 epochs of each sleep stage showed a similar pattern for all dyskinetic groups (Table 4). All types of movements were most frequent during stage awakening, followed by stages lightening and one. The movements reoccurred very occasionally in some patients during stages two and REM, and were virtually absent during slow-wave sleep, predormitory, or deepening (the median scores were zero for these four categories, with the exception of stage predormitory in patients with Gilles de la Tourette syndrome, which had a score of 2.3 movements per 100 epochs).

The Rank Order of Sleep Stages by the Frequency of Movements

Ranking of sleep stages by the proportion of epochs containing a movement showed no significant difference between the various dyskinetic groups (F = 1.000, analysis of variance [ANOVA]). The rankings were combined to give a mean rank order of sleep stages by the proportion of epochs containing a movement. Each of the following differences was significant (*P* < .05, ANOVA Duncan): Wake greater than awakening greater than lightening greater than stage 1 greater than stage 2 greater than stage REM greater than stages 3, 4, or D. Stages 3, 4, and D did not show a significant difference between each other. Stage P was less than stage 2, greater than stage 3, 4, or D, and not significantly different from stage REM.

The Timing of Movements in Relation to Awakenings and Lightenings of Sleep

Dyskinetic movements during epochs of awakening or lightening usually occurred after the onset of the change in the depth of sleep (Table 4).

The Specific EEG Phenomena Preceding Movements

All types of movement were most likely to occur after EEG evidence of arousal. Conversely, they were less likely to occur in association with sleep spindles and slow waves (Table 5).

Observations on the Consecutive Occurrence of Different Movement Conditions

Normal semipurposeful global or gestural movements were seen during the 20-second epoch before 28% of dyskinetic movements. Two patients had periodic movements of sleep and Parkinson's disease. Both cases had episodes of hand tremor that commenced during a triple flexion of a lower limb (Fig 2). On the few occasions that dyskinetic movements were manifest during epochs staged as REM sleep, they were usually preceded by a fragmentary myoclonic twitch or burst of submentalis activity (Fig 3).

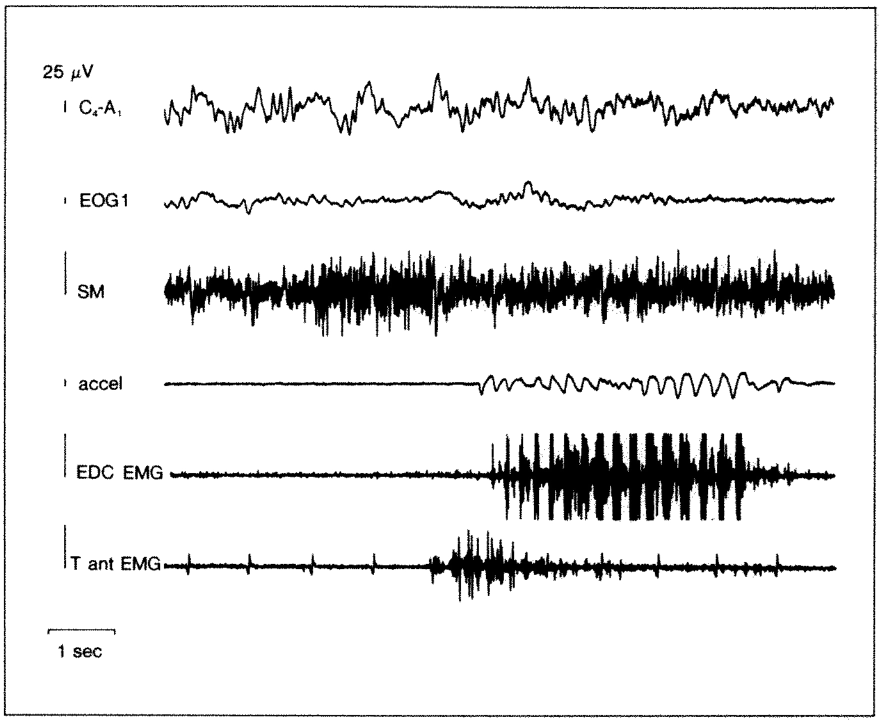

Fig 2.—An episode of parkinsonian tremor evident in the accelerometer (accel) and extensor digitorum communis (EDC) records during a lightening of sleep, preceded by evidence of arousal (K complex and increase in submental electromyogram [EMG]) and associated with a periodic movement of sleep at the onset evident in the tibialis anterior EMG (T ant EMG). REOG indicates right electro-oculogram; LEOG, left electro-oculogram; SM, submentalis surface EMG.

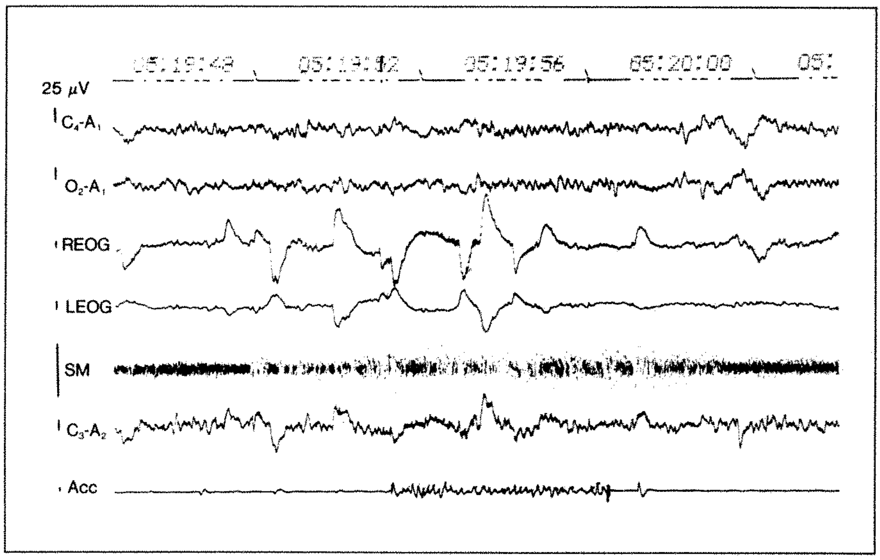

Fig 3.—An episode of tremor in a patient with Parkinson's disease during an epoch of stage rapid eye movement sleep seen in the accelerometer (Acc), and preceded by bursts of submentalis activity evident in the submental electromyographic recording. REOG indicates right electro-oculogram; LEOG, left electro-oculogram; and SM, submentalis surface electromyogram.

Observations on the Morphology of Movements in Sleep

All movements recorded by camera should have been visible to an observer from the end of the bed. Most dyskinetic movements during sleep were briefer or fragmented and of less amplitude than typical wake movements.

COMMENT

Nearly all patients with Parkinson's disease, Huntington's disease, dystonia, or Gilles de la Tourette syndrome displayed movements characteristic of the wake condition during sleep. Parkinsonian tremor, chorea, dystonic spasms, and tics all reappeared occasionally during sleep under similar circumstances. These dyskinesias occurred most commonly after an awakening and, to a lesser extent, following a shift to a lighter sleep stage or during stage one sleep. These dyskinesias were very rare during epochs staged as sleep stages two or REM, while the total number recorded during stages predormitory, deepening, three, and four was negligible. The conventional 20- or 30-second sleep staging epoch is long relative to the duration of these nocturnal movements and even the use of additional terms to describe transition epochs may not fully describe the relationship of brief movements to sleep activities such as miniarousals or other body movements. This study demonstrated that movements occurring in unequivocal sleep usually followed a 2-second epoch that contained EEG evidence of arousal. Conversely, the movements very rarely occurred in association with slow waves or sleep spindles. The latter finding is in keeping with the report of reduced motor unit activity during sleep spindles in rats.[11]

Semipurposeful movements occurred in normal subjects in the same sleep stages and in association with the same EEG phenomena as the dyskinesias. These observations suggest that both normal semipurposeful sleep movements and dyskinesias are markedly suppressed during the deeper phases. Conversely, they all reappear during awakenings, lightenings of sleep, or stage one sleep. Presumably the normal movements and dyskinesias that were studied are all generated in the brain, but it is unlikely that they arise in the same cerebral region. It is possible that sleep silences the cerebral generators in different brain regions. Alternatively, it may inactivate an output pathway from the brain to the muscles common to all these types of movement. The latter would be supported by the variety of motor behaviors that are released during REM sleep following damage to the descending inhibitory pathways arising in the region of the locus coeruleus in animals,[21] and in some patients with brain-stem disorders.[22,23] Further studies on the overall excitability of the corticospinal tract during sleep may help to clarify the nature of these mechanisms.

References

1. Lord Brain, Walton JN. Extrapyramidal disorders. In: *Brain's Diseases of the Nervous System*. London, England: Oxford University Press; 1969:513-555.
2. Spillane JD, Nathan RW, Kelly RE, Marsden CD. Painful legs and moving toes. *Brain*. 1971;94:541-556.
3. Jankovic J. The neurology of tics. In: Marsden CD, Fahn S, eds. *Movement Disorders*. 2nd ed. London, England: Butterworths; 1987:383-405.
4. Tassinari CA, Broughton R, Roger J, Gastaut H. A polygraphic study of the evolution of abnormal movements during sleep. *Electroencephalogr Clin Neurophysiol*. 1964;17:21.
5. Mano T, Shiozawa Z, Sobue I. Extrapyramidal involuntary movements during sleep. *Electroencephalogr Clin Neurophysiol*. 1982;25S:431-441.
6. Rechtschaffen A, Kales A, eds. *A Manual of Standardized Terminology and Scoring System for Sleep Stages in Human Subjects*. Washington, DC: Government Printing Office; 1968.
7. Williams RL, Karacan I, Hursch CJ. *Electroencephalography (EEG) of Human Sleep*. New York, NY: John Wiley & Sons Inc; 1974:76.
8. April R. Observations on parkinsonian tremor in all night sleep. *Neurology*. 1966;16:720-724.
9. Stern M, Roffwarg H, Duvoisin R. The parkinsonian tremor in sleep. *J Nerv Ment Dis*. 1968;147:202-210.
10. Terzano MG, Mancia D, Salati MR, Costani G, Decembrino A, Parrino L. The cyclic alternating pattern as a physiologic component of normal NREM sleep. *Sleep*. 1985;8:137-145.
11. Hongo T, Kubota K, Shimazu H. EEG spindles and depression of the gamma motor neuron. *J Neurophysiol*. 1963;26:568-580.
12. Chase MH, Morales FR. Subthreshold excitatory activity and motor neuron discharge during REM periods of active sleep. *Science*. 1983;22:1195-1198.
13. Tassinari CA, Broughton R, Poire R, Roger J, Gastaut H. An electroclinical study of nocturnal sleep in patients presenting abnormal movements. *Electroencephalogr Clin Neurophysiol*. 1965;18:95.
14. Parkinson J. *An Essay on the Shaking Palsy*. London, England: Sherwood, Neely and Jacobs; 1817.
15. Gowers WRA. *A Manual of Diseases of the Nervous System*. Philadelphia, Pa: Blakiston's; 1901.
16. Froment J, Delore P. Le tremblement parkinsonien n'est pas un tremblement de repos. *Rev Neurol*. 1927;1:46-51.
17. Friedlander WJ. Alterations of basal ganglion tremor during sleep. *Neurology*. 1952;2:222-225.
18. Forlach I, Eisen A, Fleetham J, Calne DB. Studies on dystonic torticollis during sleep. *Neurology*. 1986;36S:120.
19. Glaze DG, Frost JD, Jankovic J. Sleep in Gilles de la Tourette syndrome: disorder of arousal. *Neurology*. 1983;33:586-592.
20. Roberts R, Fitch P. Monitoring at the National Hospital, Queen Square, London. *Electroencephalogr Clin Neurophysiol*. 1985;37S:423-436.
21. Sastre JP, Jouvet M. Le comportment onirique du chat. *Physiol Behav*. 1979;22:979-989.
22. Barros-Ferreira M, Chokiewicz J, Lairy G, Salzaru P. Disorganised relations of tonic and phasic events of REM sleep in a case of brainstem tumour. *Electroencephalogr Clin Neurophysiol*. 1975;38:203-207.
23. Schenck CH, Bundlie SR, Patterson AL, Mahowald MW. Rapid eye movement sleep behavior disorder. *JAMA*. 1987;257:1786-1789.

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Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

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References:

1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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Intravenous Immunoglobulin Treatment in Patients With Chronic Inflammatory Demyelinating Polyneuropathy

Clinical and Laboratory Characteristics Associated With Improvement

P. A. van Doorn, MD; M. Vermeulen, MD; A. Brand, MD; P. G. H. Mulder, PhD; H. F. M. Busch, MD

• Of 52 patients fulfilling the criteria of chronic inflammatory demyelinating polyneuropathy, 20 (38%) did not improve after intravenous immunoglobulin treatment, two (4%) had a short-lasting improvement and subsequent infusions had no effect, nine (17%) reached a spontaneously or therapeutically induced complete remission, and 21 patients (40%) needed intermittent infusions to maintain improvement. All patients who improved initially had symptoms that significantly interfered with life-style. After treatment, 90% of these patients were independent in their daily activities. Significantly associated with improvement were disease duration of less than 1 year, progression of weakness until treatment, absence of discrepancy in weakness between arms and legs, areflexia of the arms, and slowed nerve conduction velocity of the motor median nerve. The probability of improvement if all these features are present is 93%.

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Patients with chronic inflammatory demyelinating polyneuropathy (CIDP) may respond to corticosteroids[1] and to plasma exchange,[2] which was shown in controlled studies. Improvement has also been reported after the administration of azathioprine,[3,4] cyclophosphamide,[4,5] and cyclosporine A.[6-8] Recently, several uncontrolled studies described a beneficial response to intravenous immunoglobulin (Ig) treatment.[9-13] The beneficial effect of intravenous Ig treatment in patients with CIDP was supported by the results of a double-blind placebo-controlled crossover study.[14]

In this article, we present our experience with intravenous Ig treatment in 52 patients with CIDP. The aims of this study were to investigate what the proportion of CIDP patients is that improved after intravenous Ig treatment, what the effect of repeated intravenous Ig is on the disability of these patients, and which clinical and routine laboratory factors are associated with improvement.

PATIENTS AND METHODS

Patients

Clinical and laboratory records were reviewed for all patients who were judged to have a CIDP and who were treated with intravenous Ig.

All patients included in this study fulfilled the following criteria as outlined by Dyck et al[15]: (1) the course of the disease may be steadily progressive, chronic monophasic, or recurrent; (2) nerve conduction may be normal in motor and afferent fibers, but more commonly (though not mandatory) it is slowed; (3) cyto-albuminologic dissociation is usually seen at some time during the course of the disease and in most of our patients; and (4) had a tendency to symmetric involvement and to involvement of proximal as well as distal limb muscles.

We tried to exclude patients with the Guillain-Barré syndrome,[16] therefore all patients had the clinical features of a polyneuropathy with a progression of weakness of at least 2 months. Patients with known systemic disease were excluded in our series, except for four patients with diabetes mellitus and two patients with a benign monoclonal gammopathy, type IgG-κ and IgG-λ, respectively.

Clinical Assessment

Muscle strength was tested manually using the Medical Research Council scale.[17] At least six muscle groups were tested on each side. These were muscles for shoulder abduction, elbow flexion, wrist extension, hip flexion, knee extension, and ankle dorsiflexion. Asymmetric weakness between left and right was defined as a difference of two or more grades on the Medical Research Council scale between at least one of the same muscle groups. Discrepancy in weakness between arms and legs was defined as a difference in muscle strength of two or more grades on the Medical Research Council scale between ankle dorsiflexion and wrist extension.

The disability of the patients was assessed using the Rankin scale.[18] This scale estimates functional disability or handicap. Improvement was defined as an increase of at least one step on the Rankin disability scale.

Treatment

All 52 patients with CIDP were treated with high-dose intravenous immunoglobulin (Central Laboratory of the Dutch Red Cross Blood Transfusion Service, Amsterdam, the Netherlands) in a dosage of 0.4 g/kg of body weight per day for five consecutive days. If necessary, treatment was repeated. The 52 patients did not receive corticosteroids or other immunosuppressive treatment within the 2 months before, or together with, intravenous Ig treatment.

Statistical Analysis

We investigated the association between improvement and the following characteristics: sex, age less than 50 years, disease duration less than 1 year, absence of asymmetric weakness, absence of discrepancy in weakness between arms and legs, areflexia legs, areflexia arms, progression of weakness until 4 weeks or less before onset of treatment, remitting or progressive course of the disease, cerebrospinal fluid protein level of more than 0.5 g/L in adults or more than 0.4 g/L in children, a cerebrospinal fluid white blood cell count of 10.10^6/L or less, and slowed nerve conduction velocity (NCV) of the motor median nerve. The NCV of the median nerve was measured over the forearm with standard techniques, slowed NCV was defined as an NCV of less than 80% of the lower limit of normal. The lower limit of normal was 51 m/s.

For analysis of the association between each of the above-mentioned characteristics and improvement after intravenous Ig treatment, the two-sided Fisher Exact Probability Test was used. A logistic regression analysis was used for simultaneously analyzing the predictive value of all those characteristics that were significantly related with improvement.

RESULTS

Fifty-two patients (33 men and 19 women) were diagnosed as having

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CIDP over a study period of 8 years. Their ages ranged from 5 to 82 years (mean, 48 years) at onset of CIDP in the group of patients who improved, and from 10 to 76 years (mean, 46 years) in the group of patients who did not improve.

The mean follow-up in the group of patients who improved was 4.1 years, median, 3.1 years (range, 8 to 251 months). The mean follow-up in the group of patients who did not improve was 5.7 years, median, 3.6 years (range, 16 to 295 months). Before intravenous Ig was started, nine (17%) of 52 patients had remissions and exacerbations. The mean and median time between onset of CIDP and intravenous Ig treatment in the patients with a remitting course was 9 months (range, 4 to 18 months). The mean time between onset of CIDP and intravenous Ig treatment in the patients with the progressive form was 25 months, median time, 6 months (range, 2 to 247 months). The group of patients with a remitting course has a mean age of 36 years, median, 31 years (range, 10 to 64 years). The patient group with the progressive form has a mean age of 49 years, median, 54 years (range, 5 to 82 years). Follow-up revealed lung cancer in two patients; in one patient, 6 months, in the other patient, 2 years after the diagnosis of CIDP was made and intravenous Ig was started. The second patient died. One patient died of a mesothelioma after 6 years of intravenous Ig treatment. Two patients died after a myocardial infarction, and one patient died of complications after abdominal surgery; these three patients received intravenous Ig for a period of 2 to 3 years. All six patients had improved after treatment with intravenous Ig, one had a remission after one treatment course, the other five needed repeated infusions to maintain the improved condition.

Treatment Response

Thirty-two (62%) of the 52 patients improved after treatment with intravenous Ig. The improved condition could be maintained in 30 (94%) of these patients for a mean follow-up period of 4 years. There was no correlation between the course of CIDP (remitting or progressive) and improvement after treatment with intravenous Ig. The mean time after onset of intravenous Ig treatment to the initial signs of improvement was 5 days (range, 3 to 8 days). The mean time to reach maximal improvement was 5 weeks (range, 2 to 16 weeks).

The disability before treatment and the maximal score after treatment was measured with the Rankin score (Table 1).

Table 1.—Minimal and Maximal Clinical Grade in 32 Patients With CIDP Who Improved After Intravenous Immunoglobulin (Ig) Treatment*

Rankin Score		Intravenous Ig Treatment, No. of Patients	
Level	Description	Before	After
0	Asymptomatic	. . .	7
1	Nondisabling symptoms that do not interfere with life-style	. . .	18
2	Minor disability symptoms that lead to some restriction of life-style, but do not interfere with the patients' capacity to look after themselves	. . .	4
3	Moderate disability symptoms that significantly interfere with life-style or prevent totally independent existence	12	3
4	Moderately severe disabiilty symptoms that clearly prevent independent existence, although patient does not need constant attention day and night	13	. . .
5	Severely disabled, totally dependent, requiring constant attention day and night	7	. . .

*CIDP indicates chronic inflammatory demyelinating polyneuropathy.

Four patients improved one grade, 10 patients improved two grades, eight patients improved three grades, and 10 patients improved four grades on the Rankin scale. Twenty-one (66%) of the 32 patients who improved (40% of all 52 patients) needed intermittent intravenous Ig treatment to maintain the maximal level of improvement. Initially, most of these patients received 0.4 g of intravenous Ig per kilogram of body weight every other week. In nine of these 21 patients, the dosage of intravenous Ig could gradually be tapered off to an average dosage of 0.25 g of intravenous Ig per kilogram of body weight every other week, without clinical signs of relapse. This maintenance therapy of intravenous Ig was administered within 1.5 hours in an outpatient department.

In two of 32 patients, there was a short-lasting improvement (±3 weeks), and subsequent intravenous Ig infusion had no effect. Nine (22%) of the 32 patients who improved reached complete remission (17% of all patients). The median follow-up in patients in remission was 24 months (range, 6 to 68 months). The only differences between patients who reached complete remission and the other patients who improved was the disease duration before treatment.

The median time from the first signs of CIDP to the onset of intravenous Ig treatment in the patients who reached complete remission was 3 months (range, 2 to 8 months), whereas the median time was 7 months (range, 2 to 220 months) in the group of patients who improved, but who needed intermittent intravenous Ig treatment.

Side Effects of Intravenous Ig Treatment

Minor side effects such as headache, nausea, and fatigue were sometimes observed, mainly related to the speed of infusion. None of the patients developed hepatitis. Ten patients who had intermittent intravenous Ig infusions for at least 2 years were tested for the presence of human immunodeficiency virus; all were negative.

Laboratory Data

The mean conduction velocity of the motor median nerve was 27 m/s (range, 6 to 58 m/s) in the group of patients who improved, and 44 m/s (range, 11 to 61 m/s) in patients without improvement. The mean cerebrospinal fluid protein level was 1.08 g/L (range, 0.35 to 3.41 g/L) in the group with improvement, and 1.10 g/L (range, 0.33 to 3.44 g/L) in the group without improvement. The mean number of cells in the cerebrospinal fluid in both groups was 5×10^6/L, the range in the group with improvement varied between 0 and 20×10^6/L, in the group without improvement it varied between 0 and 27×10^6/L.

Factors Associated With Improvement

Table 2 shows that five factors were significantly associated with improvement as follows: disease duration of less than 1 year, progression of weakness until approximately 4 weeks before onset of treatment, absence of

Table 2.—Clinical and Laboratory Characteristics Associated With Improvement After Intravenous Immunoglobulin (Ig) Treatment in 52 Patients With CIDP*

Descriptor	Improved After Intravenous Ig: Yes (n = 32), No. (%)	Improved After Intravenous Ig: No (n = 20), No. (%)	P†
Sex			
Male	20 (62)	13 (65)	NS
Female	12 (38)	7 (35)	NS
Age <50 y	12 (38)	11 (55)	NS
Disease duration <1 y	28 (88)	8 (40)	.0005
Progression of weakness until ≤4 wk before onset of treatment	32 (100)	14 (70)	.002
Remitting course	6 (19)	3 (15)	NS
Absence of asymmetric weakness	30 (94)	16 (80)	NS
Absence of discrepancy weakness between arms and legs	30 (94)	8 (40)	.0001
Areflexia, arms	27 (84)	6 (30)	.0001
Areflexia, legs	28 (88)	14 (70)	NS
Nerve conduction velocity in motor median nerve <80% of normal	27 (84)	8 (40)	.002
Cerebrospinal fluid protein level >0.50 g/L	30 (94)	18 (90)	NS
Cerebrospinal fluid cells ≤10.10⁶/L	27 (84)	19 (95)	NS

*CIDP indicates chronic inflammatory demyelinating polyneuropathy; NS, not significant.
†Fisher's Exact Test; two-sided.

Table 3.—Logistic Regression Model for Chance of Improvement After Intravenous Immunoglobulin (Ig) Treatment*

Factor		Odds Ratio	Logistic Coefficient	P
Absence of discrepancy in weakness between arms and legs	(a)	6.664	1.897	.076
Disease duration <1 y	(b)	6.234	1.830	.041
Areflexia, arms	(c)	4.138	1.420	.102
Nerve conduction velocity in motor median nerve <80% of normal	(d)	3.284	1.189	.199

*Probability of responding to intravenous Ig if factors a, b, c, and d are all present = $1/(1 + e^{-y}) = 0.93$. $y = C_o + C_a + C_b + C_c + C_d = 2.556$. C_o = constant term = −3.780. $C_{a,b,c,d}$ are the logistic coefficients of factors a, b, c, and d.

discrepancy in weakness between arms and legs, areflexia of the arms, and slowed NCV of the motor median nerve over the forearm.

Since the factor "progression of weakness until onset of treatment" was required for improvement, we excluded this factor from further analysis.

Using logistic regression, the other four factors significantly associated with improvement were analyzed and the predictive value of these factors combined was calculated (Table 3). This table shows that if the factors absence of discrepancy in weakness between arms and legs, disease duration less than 1 year, areflexia of the arms, and slowed NCV over the motor median nerve are present, the estimated probability of improvement is 93%. If none of these factors is present, the estimated probability is 2%.

The first two factors are the strongest predictive factors, but the last one "slowed motor median NCV" still has a clinically relevant contribution to the probability of improvement, since the odds ratio is 3.284.

Patients Without Improvement

Twenty (38%) of 52 patients with CIDP did not improve after intravenous Ig treatment. Fifteen of these 20 patients were treated with prednisone, and five improved. After tapering off prednisone, one of these five patients was treated with azathioprine, which was followed by improvement. Five patients were not treated with prednisone; one patient showed a slow spontaneous improvement without further treatment, and the four other patients were not treated with prednisone because side effects were feared. One of the two patients with short-lasting improvement after treatment with intravenous Ig had a favorable response to prednisone. The second patient did not respond to treatment with prednisone, azathioprine, or cyclophosphamide. This patient improved after plasma exchange and treatment with cyclosporine A. After 3 years, this patient is in Rankin scale three.

We reviewed the case records and the follow-up information of the 20 patients who had not improved after intravenous Ig, and tried to find a diagnosis other than CIDP. Two patients might have a polyneuropathy of the type as described by McLeod et al,[20] and one patient might have vasculitis limited to the peripheral nervous system.[21] In two patients the polyneuropathy was associated with mild diabetes mellitus and in one patient with alcohol abuse. Three patients had a polyneuropathy that could have been initially a neuropathy as described by Pestronk et al[22]; in the serum samples of these three patients high titers of anti-GM_1 antibodies were demonstrated. In one patient a hereditary polyneuropathy was likely. In the 10 other patients, no diagnosis could be established other than CIDP.

COMMENT

This study shows that 38% of patients judged to have a CIDP did not improve after treatment with intravenous Ig. A further 4% had a short-lasting improvement and subsequent infusions had no effect. A complete remission was reached by 17% of patients, which might have been caused by treatment, but spontaneous remissions do occur and some patients may have had a Guillain-Barré syndrome-like course even after progression of more than 8 weeks. Especially in this group of patients it is difficult to decide whether or not these patients had responded to treatment. A beneficial treatment response is more likely in the patients (40%) who improved after treatment with intravenous Ig, and who needed intermittent infusions to maintain the improved condition.

Intravenous Ig treatment was not accompanied by serious side effects. None of the patients developed hepatitis. In 10 patients who had been treated at regular intervals for at least 2 years, human immunodeficiency virus antibodies could not be demonstrated.

One of the major advantages of treatment with intravenous Ig in comparison with prednisone is that improvement begins immediately. This is clearly demonstrated when we compare our results with that of a study in 60 patients[23] treated with 100 mg of prednisone daily for 2 to 4 weeks, followed by an alternate-day single dose of 100 mg until the clinical improvement reached a plateau phase. In that study the mean time for initial improvement was 1.9 months (mean time after treatment with intravenous Ig only 5 days), and the mean time to reach a clinical plateau was 6.6 months (after Ig only 5 weeks).

To maintain the improved condition,

40% of the patients needed intermittent intravenous Ig infusions every other week. We tried various schedules of reduction of the intravenous Ig dosage. We had more favorable results with tapering off the infusion dosage than with increasing the interval between the infusions. In nine of 21 patients, the dosage could be reduced to 0.25 g of intravenous Ig per kilogram of body weight every other week. Maintenance treatment with intravenous Ig is expensive. This treatment has to be compared with plasma exchange and to prednisone, which is the standard treatment in CIDP. There is no study that shows what the maintenance dosage of prednisone usually is and what the side effects are of long-term prednisone treatment in CIDP. It is reasonable to assume that the side effects of prednisone treatment in myasthenia gravis are not much different from CIDP. It has been estimated that approximately 25% of patients with myasthenia gravis develop serious side effects within 4 years of treatment with prednisone.[24] Prolonged plasma exchange has not been associated with any complications except anemia,[21] is about as expensive as intravenous Ig treatment, but is inconvenient for the patient.

Chronic inflammatory demyelinating polyneuropathy, according to the criteria outlined by Dyck et al,[15] is difficult to distinguish from some other neuropathies. The first neuropathy to consider has been described by McLeod et al.[20] This neuropathy is a slowly progressive axonal degeneration of undetermined cause. The characteristic history is that of a gradual onset of numbness, tingling, coldness, or burning sensation in the feet and hands, weakness of the legs, and, less commonly, weakness of the hands. Neurological examination may demonstrate distal muscle wasting and weakness in the lower limbs that may be quite pronounced. In McLeod and coworkers' series of patients, one third had areflexia of the legs, but total areflexia was less common. The cerebrospinal fluid protein level was often slightly elevated and the NCVs were slightly reduced and sometimes reached values that suggested a demyelinating neuropathy. If these patients are seen late in the course of the disease, distinction from CIDP may be difficult.

A second neuropathy that may be difficult to distinguish from CIDP is the nonsystemic vasculitic neuropathy.[21] The course in these patients may be stepwise progressive and thereafter static for a time. These patients may have severely affected legs and no or slight involvement of the arms.

Finally, CIDP may be confused with multifocal motor neuropathy. In the patients described by Pestronk et al,[22] asymmetrical weakness developed in one arm and progressed over 2 to 3 years to involve the other arm, legs, and trunk. High titers of antibodies to GM_1 ganglioside were demonstrated in these patients. These patients do not necessarily have areflexia of the arms or slowed NCV of the motor median nerve over the forearms. Initially, three of our patients had a similar course and in serum samples withdrawn at the beginning of the disease we could demonstrate high titers of antibodies to GM_1. These three patients did not respond to intravenous Ig.

We conclude that several factors that can be taken together as a progressive neuropathy of relatively short duration with clearly affected arms are associated with improvement after intravenous Ig treatment, and that the presence of these factors may have consequences for the choice of treatment in patients with CIDP.

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References

1. Dyck PJ, O'Brien PC, Oviatt KF, et al. Prednisone improves chronic inflammatory demyelinating polyradiculoneuropathy more than no treatment. *Ann Neurol.* 1982;11:136-141.
2. Dyck PJ, Daube J, O'Brien P, et al. Plasma exchange in chronic inflammatory demyelinating polyradiculoneuropathy. *N Engl J Med.* 1986;314:461-465.
3. Pentland B, Adams GGW, Mawdsley C. Chronic idiopathic polyneuropathy treated with azathioprine. *J Neurol Neurosurg Psychiatry.* 1982;45:866-869.
4. Dalakas MC, Engel WK. Chronic relapsing (dysimmune) polyneuropathy: pathogenesis and treatment. *Ann Neurol.* 1981;9(suppl):134-145.
5. Fowler H, Vulpe M, Marks G, Egolf C, Dau PC. Recovery from chronic progressive polyneuropathy after treatment with plasma exchange and cyclophosphamide. *Lancet.* 1979;2:1193.
6. Kolkin S, Nahman NS, Mendell JR. Chronic nephrotoxicity complicating cyclosporine treatment of chronic inflammatory demyelinating polyradiculoneuropathy. *Ann Neurol.* 1986;20:146.
7. Tindall RSA, Hall K, Rollins JA. Cyclosporine in the treatment of chronic inflammatory demyelinating polyneuropathy: a pilot study in steroid dependent or steroid resistant patients. Immunointervention in autoimmune diseases, Paris, France, June 1988. Workshop 19 (demyelinating diseases).
8. Jongen PJH, Joosten EMG, Gabreels-Festen AWM. Alternating cyclosporine and high dose prednisone therapy in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) not responding to conventional long term immunosuppression. Immunointervention in autoimmune diseases, Paris, France, June 1988. Workshop 19 (demyelinating diseases).
9. Vermeulen M, van der Meché, Speelman JD, Weber A, Busch HFM. Plasma and gamma-globulin infusion in chronic inflammatory polyneuropathy. *J Neurol Sci.* 1985;70:317-326.
10. Albama M, McNamara ME, Sokol M, Wijshock E. Improvement of neurologic function in chronic inflammatory demyelinating polyradiculoneuropathy following intravenous gammaglobulin infusion. *Arch Neurol.* 1987;44:248-249.
11. Cook JD, Delgrado MR, Soutter-Glass D. Treatment of childhood autoimmune polyneuropathy, IV: gamma globulin. *Neurology.* 1987;37 (suppl 1):253.
12. Curro Dossi B, Tezzon F. High-dose intravenous gammaglobulin for chronic inflammatory demyelinating polyneuropathy. *Ital J Neurol Sci.* 1987;8:321-326.
13. Fead JM, Day B, Pollock M, Taylor PK, Nukada H, Hammond-Tooke GD. High-dose intravenous human immunoglobulin in chronic inflammatory demyelinating polyneuropathy. *Neurology.* 1989;39:422-425.
14. van Doorn PA, Brand A, Strengers PFW, Meulstee J, Vermeulen M. High-dose intravenous immunoglobulin treatment in chronic inflammatory demyelinating polyneuropathy. A double blind placebo controlled cross-over study. *Neurology.* 1990;40:209-212.
15. Dyck PJ, Lais AC, Ohta M, et al. Chronic inflammatory demyelinating polyradiculoneuropathy. *Mayo Clin Proc.* 1975;50:621-637.
16. Asbury AK, Arnason BGW, Karp HR. Criteria for the diagnosis of Guillain-Barré syndrome. *Ann Neurol.* 1978;3:565-566.
17. *Medical Research Council Aids to the Examination of the Peripheral Nervous System.* London, England: Her Majesty's Stationery Office; 1976.
18. van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, van Gijn J. Interobserver agreement for assessment of handicap in stroke patients. *Stroke.* 1988;19:604-607.
19. Dyck PJ. Intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy and in neuropathy associated with IgM monoclonal gammopathy of unknown significance. *Neurology.* 1990;40:327-328.
20. McLeod JG, Tuck RR, Pollard JD, Cameron J, Walsh JC. Chronic polyneuropathy of undetermined cause. *J Neurol Neurosurg Psychiatry.* 1984;47:530-535.
21. Dyck PJ, Benstead TJ, Conn DL, Stevens JC, Windebank AJ, Low PA. Nonsystemic vasculitic neuropathy. *Brain.* 1987;110:843-854.
22. Pestronk A, Cornblath DR, Ilyas AA, et al. A treatable multifocal motor neuropathy with antibodies to GM_1 ganglioside. *Ann Neurol.* 1988; 24:73-78.
23. Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy: clinical characteristics, course, and recommendations for diagnostic criteria. *Arch Neurol.* 1989;46:878-884.
24. Oosterhuis HJGH. Myasthenia gravis. In: *Clinical Neurology and Neurosurgery.* New York, NY: Churchill-Livingstone Inc; 1984;5:175-208.

Posttraumatic Torticollis

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• We report six cases of torticollis precipitated by neck trauma. The dystonia began 1 to 4 days after the trauma and differed clinically from idiopathic torticollis by marked limitation of range of motion, lack of improvement after sleep ("honeymoon period"), and absence of *geste antagonistique.* Worsening with action was not present; nor was there improvement with support as seen with idiopathic torticollis. Onset of pain immediately after the trauma and marked spasms of the paracervical muscles were other predominant features. Anticholinergic therapy was without benefit; however, some improvement occurred with botulinum toxin injection. It is concluded that torticollis can be caused by peripheral trauma and that it has unique clinical characteristics.

(*Arch Neurol.* 1991;48:221-223)

Torticollis is a focal dystonia characterized by twisting contraction of the neck muscles, resulting in forced turning of the head. An etiologic factor can rarely be identified for most cases of focal dystonia, although many secondary causes have been described.[1] Trauma, either to the basal ganglia structures[2] or peripherally to somatic regions, has been proposed as a cause of dystonia.[3,4] We report cases of torticollis that abruptly followed trauma to the neck, and describe the resultant clinical features.

REPORT OF CASES

Case 1.—A 39-year-old man was injured by a blow to the right side of his neck with a steel plate without injury to his head or loss of consciousness. He continued his work despite the severe pain in his neck, shoulder, and throat. On awakening the next morning, his head turned to the right. He was thought to have a whiplash injury producing a temporary "wryneck." However, the disorder persisted without improvement. For 6 months he received diazepam, which did not provide relief. Cervical roentgenograms, including odontoid views, were normal. A myelogram showed protruding disks at the C-4-C-5 and C-5-C-6 levels, and the patient underwent laminectomy and arthrodesis. The procedure, however, was without benefit. Subsequent trials of anticholinergic drugs and other medications were ineffective.

When examined 4 years after the accident, the patient presented the same features of torticollis that had developed the day after his injury. His chin turned to the right, with his head tilted to the left and shifted anteriorly; his left shoulder was elevated. Torticollis was present with or without head support; it worsened during standing and walking. The constant deviation of the patient's head did not allow movement past the midline, and he could not touch his right shoulder with his chin. There was severe pain in the region of the hypertrophic neck muscles that were involved in the turned neck posture (primarily, the right splenus capitis and the left sternocleidomastoid). The patient had not found any maneuvers or tricks to lessen the severity of the torticollis, nor was there relief when he rested his head against the wall. The neck posture returned to normal during sleep. On awakening each morning, he also reported a period of approximately 20 minutes when his torticollis was less severe.

The findings of the remainder of his neurologic examination were normal. Treatment with botulinum toxin led to marked improvement of neck posture, muscle hypertrophy, and pain.

Case 2.—A 47-year-old man was carrying a long 45-kg (100-lb) bar, when he lost his grip and tried to catch it with his right hand. He heard a "pop" and "crack" from the left side of his neck and shoulder and felt immediate pain in the upper part of his shoulder and the lateral aspect of his neck, with numbness throughout his left arm. The next day he awoke with his head pulling toward the right. The right splenius capitis, right upper trapezius, right sternocleidomastoid, and left scalene muscles contributed prominently to the pulling of his neck. He was unable to turn more than 30° to either the right or the left. He had not found any trick maneuvers to lessen the torticollis. His condition did not improve during sleep. His only other neurologic abnormality was a preexisting horizontal diplopia.

When the patient was seated, there was a tendency for his head to pull to the right, with his chin slightly elevated. Intermittently, there were tonic contractions lasting several seconds, which involved the left platysma, the right and left sternocleidomastoid, and the left trapezius muscles. Otherwise, the findings of the rest of his neurologic examination were normal. Cervical roentgenograms, including odontoid views; a computed tomographic (CT) scan of the head; and a cervical myelogram were normal. The patient was started on a course of trihexyphenidyl hydrochloride, without improvement. He declined further treatment.

Case 3.—A 27-year-old woman fell, striking her head and neck against the open door of a dishwasher. There was no loss of consciousness. The patient experienced immediate pain and muscle spasm. Her neck started to pull to the right within 2 days of the accident. Cervical roentgenograms and a CT scan of the patient's head and neck were normal. On examination 10 months

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Clinical Characteristics of Posttraumatic Torticollis*

Patient No./Age, y/Sex	Family History	Onset of Pain	Onset of Torticollis, d	"Honeymoon Effect"	Improve With Sleep	Range of Motion	Action-Induced Worsening	Improve With Rest	MRI, CT, and Myelography	Anti-cholinergic Effect	RSD
1/39/M	No	Immediate	1	Yes	Yes	En bloc	Yes	No	Herniated disk at C-4-C-5, condition persisted postoperatively	No	No
2/47/M	No	Immediate	1	No	No	En bloc	Yes	No	Normal	No	No
3/27/F	No	Immediate	2	No	No	En bloc	No	No	Normal	No	No
4/19/M	No	Immediate	1	No	Yes	En bloc	No	No	Normal	No	No
5/28/F	No	Immediate	4	No	No	En bloc	No	No	Normal	No	No
6/48/F	No	Immediate	1	No	No	En bloc	No	No	Stenosis at C-5-C-6 2 y later	No	Yes

*MRI indicates magnetic resonance imaging; CT, computed tomography; and RSD, reflex sympathetic dystrophy.

after the accident, she had pure laterocollis to the right, with her head tilted 40° from the midline and marked elevation of her right shoulder. She was unable to move her head out of this position by more than 10°. She turned en bloc. There was no "honeymoon period" in the morning. According to her mother, the condition persisted during sleep. The patient has not found any tricks that would alleviate her laterocollis. Electromyography showed continuous cocontraction of the right sternocleidomastoid, right scalenus medius, and right trapezius muscles. No cocontraction was noted in the corresponding left-sided muscles. Treatment with trihexyphenidyl and clonazepam was ineffective. Botulinum toxin injection into the above-mentioned muscles resulted in mild improvement.

Case 4.—At the age of 19 years, the patient ran into a partially opened garage door with enough force to knock himself 3 m (10 ft) backward. He "saw stars" but did not lose consciousness. He had neck pain immediately after the accident. That same day, he developed torticollis to the right, with his head tilted to the left. He did not have nausea, dizziness, or vomiting after the accident. Cervical spine roentgenograms, including odontoid views; skull roentgenograms and a pneumoencephalogram were normal. A CT scan of the head performed 35 years later was also normal. A multilevel posterior cervical rhizotomy performed in 1985 resulted in partial, temporary relief. The patient has not had any benefit from anticholinergic medications or clonazepam. Examination 38 years after the accident revealed torticollis with torsion to the right at 30°, tilting of the head to the left at 35 degrees, and moderately severe left shoulder elevation. Deviation occurred constantly. There were no trick movements that would alleviate the torticollis. His range of motion was limited to within 15° of the primary head position. He denied any honeymoon effect in the morning. He turned his body en bloc, with little mobility of the neck. According to his wife, his neck improved during sleep. Electromyographic studies revealed continuous cocontraction of the left sternocleidomastoid, left scalenus medius, left levator scapulae, left trapezius, left deep retrocollis, and bilateral splenus capiti muscles. Botulin injection into the above-mentioned muscles resulted in moderate improvement.

Case 5.—A 28-year-old woman was involved in two car accidents. In the first accident, her car was hit from the back as she was about to turn left. She heard a "snap" in her neck. She had the feeling of a stiff neck. At the emergency department, nothing was found in the cervical roentgenograms, and the patient was treated with cyclobenzaprine hydrochloride as well as a cervical collar. On the way home, her car struck the back of a van that pulled in front of her. She was seen again in the emergency department, and a second series of cervical roentgenograms did not demonstrate any abnormality. Because of her medication, the patient was drowsy for the first 3 days. On the fourth day, she noticed some pulling in the left side of her neck, and the previous stiffness increased. When examined by us, her neck was pulled fully to the left. She was unable to move her neck from this position. She would turn her body en bloc when she needed to turn to either side. She was not aware of any trick that would straighten her neck. She denied any honeymoon period in the morning. She also had pain in her left shoulder. Holding her head in a lateral position decreased her pain. Her laterocollis persisted during sleep. There was marked cocontraction of the left sternocleidomastoid and left scalenus medius muscles. Cervical spine roentgenograms, including odontoid views and those obtained during extension and flexion, odontoid view and CT scans of the spine did not reveal any abnormality. Botulinum toxin injection into the left sternocleidomastoid and scalenus medius muscles resulted in moderate improvement.

Case 6.—A 48-year-old woman developed torticollis after an accident in which she hit the top of her head against the roof of her car. Pain in her neck developed 1 day after the accident. This area became increasingly painful, and the patient had increasing difficulty in turning her neck from side to side. She did not have any tricks that would alleviate her torticollis. A bone scan, a magnetic resonance imaging scan, and a roentgenogram of the cervical spine obtained shortly after the accident were normal. Another magnetic resonance imaging scan performed 2 years later showed a stenosis at the C-5-C-6 level. The patient developed pain in her right arm; the pain started from the middle of the back of her head and radiated to the fourth and fifth fingers. She described a feeling of tingling, numbness, and coldness in her right hand. She felt coldness in her left foot. The findings of electromyography performed a few months after the accident were normal. The patient was hospitalized twice for excessive pain. A cervical myelogram obtained 1 year after the accident showed extensive degenerative arthritis throughout the neck and lumbar spine, with mild encroachment of the subarachnoid space and flattening of the spinal cord. Cervical CT showed narrowing of the anteroposterior diameter of the spinal canal at the C-5-C-6 level. The patient's medical history was remarkable for hypothyroidism and an L-4-L-5 disk operation 10 years previously. Neurologic examination revealed weakness of flexion and extension of the lower part of the left leg and the left ankle. The right shoulder, right arm, and left leg were cold and slightly cyanotic. Deep tendon reflexes were brisk bilaterally but more pronounced in the lower part of the left leg. Toes were down going. Pinprick sensation was decreased in the lower part of the left leg. Pronator drift was observed in the right arm. The patient's head tilted forward and to the left, and her chin was pointed to the right. Range of motion, which was decreased to 30° on each side, did not improve with lying down. The condition persisted during sleep. There was mild prominence of the right splenus capitis and left sternocleidomastoid muscles. The diagnosis of posttraumatic torticollis, cervical stenosis, and reflex sympathetic dystrophy was made. Anticholinergic medication had no benefit. However, treatment with botulinum toxin was helpful.

COMMENT

Suchowersky and Calne[5] described a case of torticollis following trauma to the neck. The patient involved developed torticollis 2 weeks after the initial event owing to atlantoaxial dislocation. None of our patients had subluxation as evidenced by cervical spine roentgenograms, including odontoid views, or by cervical CT. Brin et al[3] mentioned four patients with neck and shoulder injury who developed torticollis 12 hours to 8 weeks after the injury, and suggested that dystonia precipitated by peripheral injury may represent the clinical response to sensory perturbation on the extrapyramidal motor pathways via axonal sprouting. Jankovic and Van der Linden[6] described 17 patients with peripheral trauma prior to the onset of dystonia; one of them had torticollis. The preceding injuries occurred 1 day to 10 months before the onset of the dystonia. Sheehy and Marsden[7] noted that three cases in their series of 60 patients had a traumatic preceding event. They did not report the time relationship between the injuries and the occurrence of torticollis. In our patients, the torticollis began within 1 to 4 days of the traumatic events. The immediate onset of pain after the trauma and preceding the torticollis is of interest. Our cases did not reveal any pathology, despite intensive diagnostic studies. All patients were healthy prior to the incidents. Three patients heard cracking in their necks at the moment of the injuries. Furthermore, in contrast to previous reports, there was no history of familial neurologic disorders in our cases. In idiopathic torticollis, there is cocontraction of synergistic muscles, such as the sternocleidomastoid and the contralateral splenus capitis, resulting in twisting of the head. Patients with idiopathic torticollis are generally able to turn their heads easily in the same direction of the dystonic posture, although turning to the opposite side may be difficult. In our six cases, there was marked decrease in range of motion, and the patients were unable to turn their heads to either side. This relative fixation of the neck maybe a diagnostic clue for trauma-induced torticollis (Table). Although not reported by Suchowersky and Calne,[5] this fixation was also seen in their patient (O. Suchowersky, MD, oral communication, November 1989). This diagnostic clue, however, has also been seen by one of us (D.D.T.) in psychogenic torticollis. Psychogenic movement disorders often betray themselves through frequent change of symptoms, inconsistency over time, or incongruency with the classical dystonia.[8] In contrast, in our patients, the symptoms were unchanged and consistent over time. Another diagnostic clue is the report by four of our six patients that their torticollis persisted during sleep, in contrast to idiopathic torticollis, which often disappears. The clinical picture also differed from idiopathic torticollis in that a honeymoon period was not seen in our patients. Although this is not always present, patients with idiopathic torticollis frequently have a short episode of improvement each morning on awakening. The majority of our patients with trauma-induced torticollis did not improve with rest or support. But they also did not worsen with action, as is seen with idiopathic torticollis. The above-mentioned features may favor the classification of "nondystonic" torticollis in our patients. None of them responded to anticholinergics. Owing to the short follow-up of our cases (except cases 1 and 4), no statement can be made about remission. Jankovic and Van der Linden[6] analyzed 17 patients with dystonia occurring after trauma. Possible predisposing factors include exposure to neuroleptics, personal and family history of dystonia, essential tremor, prematurity, or developmental delay.[6] These predisposing factors were lacking in our cases, which may imply direct effect of the peripheral trauma. As with other acquired disorders, an aggressive search for cause should be initiated. In conclusion, the clinical picture of torticollis induced by peripheral trauma can be differentiated from its dystonic counterpart by the following features: decreased range of neck motions; persistence during sleep and head support; symptoms unchanged with action; and lack of family history, honeymoon period, and *geste antagonistique.*

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References

1. Calne DB, Lang AE. Secondary dystonia. In: Fahn S, Marsden CD, Calne D, eds. *Dystonia 2.* New York, NY: Raven Press; 1988:9-33.
2. Brett EM, Hoare RD. Progressive hemi-dystonia due to focal basal ganglia lesion after mild head trauma. *J Neurol Neurosurg Psychiatry.* 1981;44:460.
3. Brin MF, Fahn S, Bressman SB, Burke RE. Dystonia precipitated by peripheral trauma. *Neurology.* 1986;36(suppl 1):119.
4. Schott GD. The relationship of peripheral trauma and pain to dystonia. *J Neurol Neurosurg Psychiatry.* 1985;48:698-701.
5. Suchowersky O, Calne DB. Non-dystonic cause of torticollis. *Adv Neurol.* 1988;50:501-508.
6. Jankovic J, Van der Linden C. Dystonia and tremor induced by peripheral trauma: predisposing factors. *J Neurol Neurosurg Psychiatry.* 1988;51:1512-1519.

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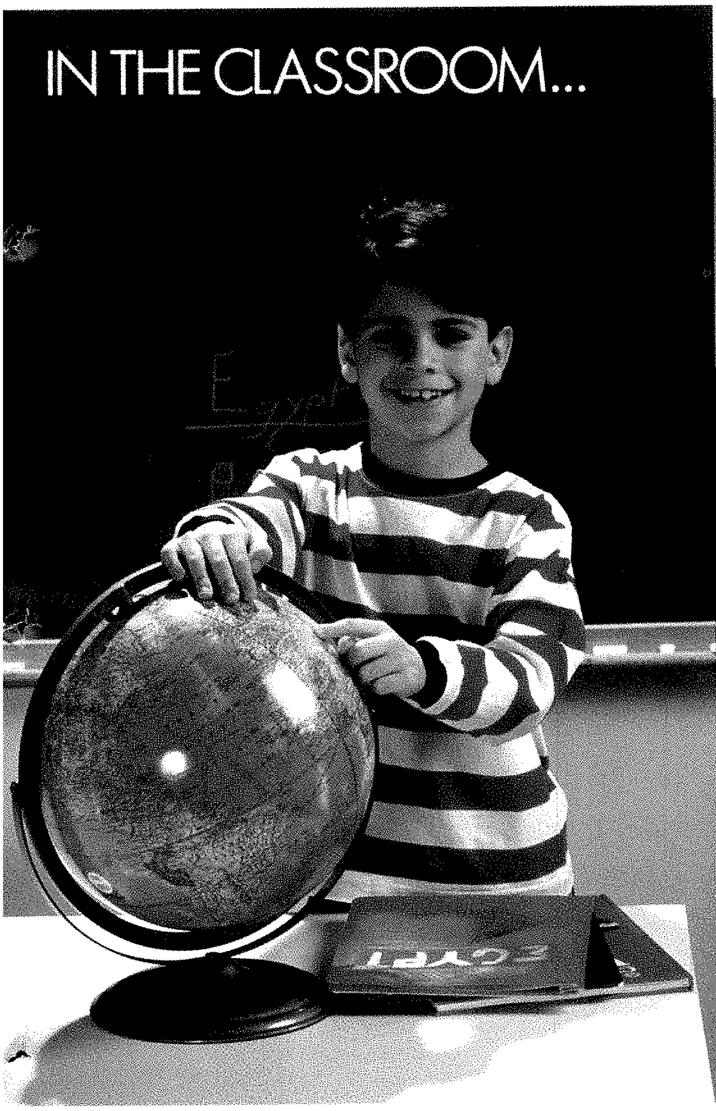
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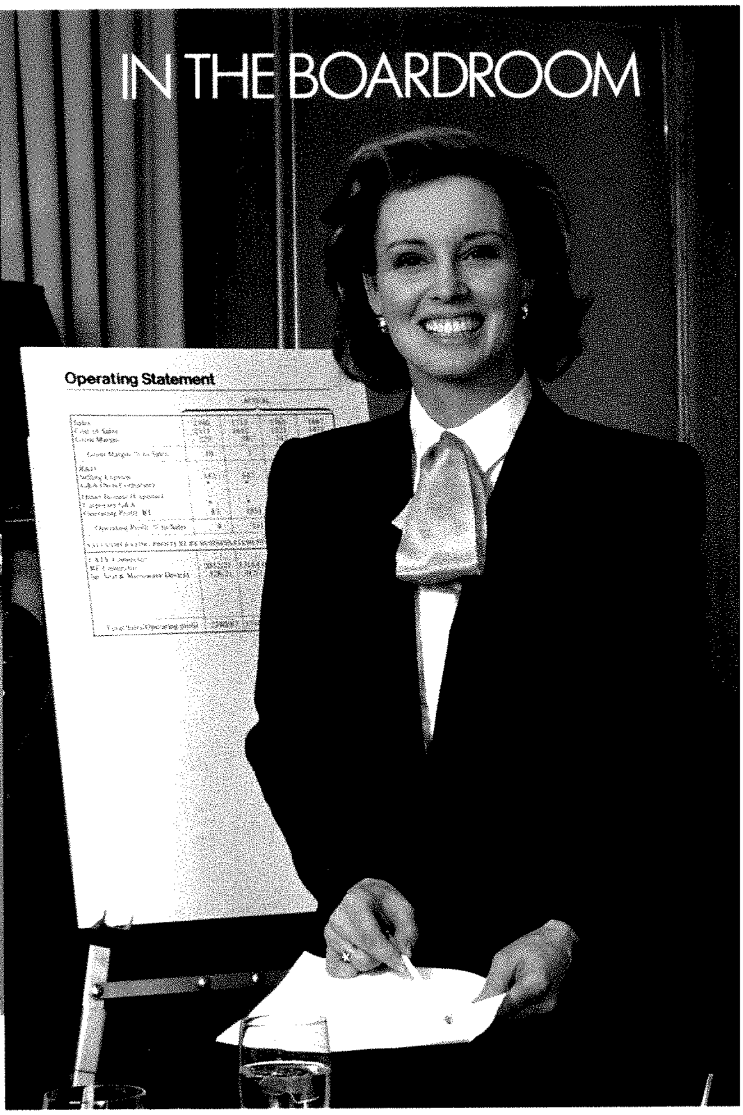

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References

1. Smith DB, Mattson RH, Cramer JA et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58
2. Mattson RH, Cramer JA, Collins JF et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151
3. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;29:794-804

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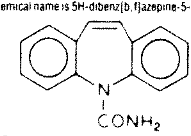

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It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

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2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

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Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

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WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

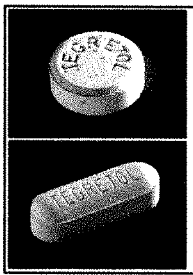
It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System. Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin. Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary.

Cardiovascular System. Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver. Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System. Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System. Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System. Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System. Aching joints and muscles, and leg cramps.

Metabolism. Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration. Irregular breathing, respiratory depression.

Cardiovascular System. Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles. Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract. Nausea, vomiting.

Kidneys and Bladder. Anuria or oliguria, urinary retention.

Laboratory Findings. Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning. When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug. Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption. Activated charcoal, laxatives.

Measures to Accelerate Elimination. Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression. Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock. Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions. Diazepam or barbiturates.

Warning. Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities. If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak*—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture.

Dispense in tight container (USP).

Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles.

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Chemotherapy for Oligodendroglioma

Progress Report

J. Gregory Cairncross, MD, David R. Macdonald, MD

Six years ago, we began to notice that recurrent oligodendrogliomas, tumors that had regrown after one or more surgeries and radiotherapy, responded to chemotherapy. These tumors were clinically aggressive, contrast-enhancing, histologically anaplastic, and relatively pure. We concluded, after eight consecutive responses (see reference 1 for response criteria),[1] that anaplastic oligodendroglioma was a chemosensitive tumor.[2] In this article, we review our experience with chemotherapy for this uncommon brain tumor.

Table 1.—Summary of Treatment and Response: 'First' Recurrence*

Patient No.	Adjuvant Chemotherapy	Sites of Recurrence		Chemotherapy for "First" Recurrence	Response Assessment		Response Duration, mo
		Brain	Systemic		Brain	Systemic	
1	−	+	+	Carmustine	PR	CR	16
2	−	+	−	PCV	CR	. . .	18
3	Diaziquone	+	+	PCV	PR	CR	14
4	Carmustine	+	−	Diaziquone	PR	. . .	36
5	−	+	−	Fludarabine	PD	. . .	. . .
				PCV	PR	. . .	8
6	−	+	−	PCV	PR	. . .	13
7	−	+	−	PCV	PR	. . .	8
8	−	+	−	Diaziquone	PD	. . .	. . .
				PCV	PR	. . .	19
9	−	+	−	PCV	CR	. . .	34
10	Diaziquone	−	+	PCV	. . .	PR	8

*Prior surgery and radiotherapy. CR indicates complete response; PR, partial response; PD, progressive disease; minus sign, none or not applicable; plus sign, present; and PCV, a drug combination that includes procarbazine, lomustine (CCNU), and vincristine.

Table 1 summarizes the results of treatment for "first" recurrence. We have treated 10 patients, all have responded; two completely and eight partially. Patient 1 responded to carmustine (BCNU), patient 4 to diaziquone (AZQ), the others to a drug combination (PCV) that included procarbazine, lomustine (CCNU), and vincristine.[3] (Patient 5 failed to respond to fludarabine, patient 8 to diaziquone; both responded to PCV.) The median duration of response is 15 months (range, 8 to 36 months). All patients have relapsed (patients 5, 7, and 10 relapsed while receiving PCV; the others had late relapses). We think PCV (Table 2) is particularly effective chemotherapy for anaplastic oligodendroglioma, but other drugs or drug combinations may prove superior. Recently, Levin et al[4] reported that PCV is superior to carmustine in the treatment of newly diagnosed anaplastic glioma—a testament to its effectiveness for moderately aggressive glial tumors.

Patients with recurrent oligodendroglioma respond to chemotherapy, especially PCV, but are not cured. We have re-treated seven patients with "salvage" chemotherapy. Table 3 summarizes the results of treatment for second recurrence. Diaziquone and cisplatin were ineffective, but PCV and intravenous melphalan yielded partial responses. Patient 4 had a sustained partial response to PCV despite two prior chemotherapy programs; carmustine adjuvantly (ie, at diagnosis) and diaziquone at first recurrence. Experience with patient 4 indicates that some patients with recurrent oligodendroglioma will respond to a nitrosourea-based regimen (eg, PCV) even though treated previously with nitrosoureas. Extrapolating, some PCV responders may at relapse respond again to PCV. Inadequate bone marrow reserve precluded further chemotherapy for patient 4. Patients 7 and 8 had brief partial responses to intravenously administered melphalan. Inadequate bone marrow reserve limited our ability to give full doses, and may have compromised treatment.

In oncology, when an effective therapy for recurrent tumor is recognized, longer survival and some cures have followed aggressive treatment at diag-

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Table 2.—PCV Chemotherapy Regimen

Drug(s)	Dosage and Schedule	Frequency
Lomustine	110 mg/m² orally; day 1	Every 8 wk
Vincristine*	1.4 mg/m² intravenously; day 8	
Procarbazine	60 mg/m² per day orally; days 8 through 21	
Vincristine*	1.4 mg/m² intravenously; day 29	

*Maximum dose, 2 mg.

Table 3.—Summary of Treatment and Response: Second Recurrence*

Patient No.	Sites of Relapse		Chemotherapy for Second Recurrence	Response Assessment		Response Duration, mo
	Brain	Systemic		Brain	Systemic	
1	+	+	Diaziquone	PD	PD	...
2	+	–	...	...	...	...
3	+	+	Cisplatin	PD	PD	...
4	+	+	PCV	PR	PR	12
5	+	–	Cisplatin	PD	...	...
6	+	–	Diaziquone	PD	...	...
			Cisplatin	PD	...	...
7	+	–	Melphalan	PR	...	3
8	+	–	Melphalan	PR	...	2
9	–	–	...	...	...	...
10	–	+	...	...	...	...

*PD indicates progressive disease; PR, partial response; minus sign, none, not applicable, or no response; plus sign, present; and PCV, a drug combination that includes procarbazine, lomustine (CCNU), and vincristine.

Table 4.—Results of Chemotherapy Before Radiotherapy for Oligodendroglioma

Patient No.	Chemotherapy Regimen*	Courses (No.) Pre-Radiotherapy†	Response to Chemotherapy	Duration of Response, mo‡
1	PCV	5	Complete response	34§
2	PCV	2	Complete response	31§
3	PCV	4	Partial response	28§

*PCV indicates a drug combination that includes procarbazine, lomustine (CCNU), and vincristine.
†Focal radiotherapy after response induction field based on preoperative computed tomographic scan.
‡Includes radiotherapy.
§Continued response.

nosis. Encouraged by successful chemotherapy for recurrent oligodendroglioma, we have treated three newly diagnosed patients with PCV prior to radiotherapy and again observed responses; two complete and one partial (Table 4). These patients had residual or progressive tumor after initial surgery.[5] This approach to initial treatment is feasible and effective. It may or may not be superior to radiotherapy alone or other early treatment strategies. Intensive initial treatment seems logical, but we are proceeding cautiously because, for oligodendroglioma, there is concern that aggressive behavior cannot always be reliably predicted by histologic findings. Potentially toxic treatment may be inappropriate for indolent gliomas.[6]

Reports on small numbers of patients from single institutions may overestimate the effectiveness of "new" treatments. Accordingly, the National Cancer Institute of Canada's Clinical Trials Group is conducting a multicentered phase II study of "intensive PCV" for oligodendroglioma. Patients with measurable, newly diagnosed or recurrent, contrast-enhancing, relatively pure, anaplastic oligodendroglioma are eligible. This study will confirm, modify, or refute our findings and examine the pros and cons of a dose-escalated regimen.

The Central Nervous System Cancer Consortium, led by Schold, conducted a phase II study of intravenously administered melphalan for recurrent anaplastic glioma and observed that patients with oligodendroglioma were more likely to respond (55%) than those with nonoligodendroglioma (11%).[7] This important finding, and an interesting case report by Saarinen et al,[8] are further evidence that aggressive oligodendroglioma is a chemosensitive tumor. The Consortium has accrued additional patients with oligodendroglioma to this study and will report a definitive analysis of intravenously administered melphalan.

While documenting effective chemotherapy for recurrent oligodendroglioma, responses to chemotherapy prior to radiotherapy in new patients, and long survival compared with other malignant gliomas,[9] we observed systemic metastasis (patients 1, 3, 4, and 10 in this article, and three others[10]), hitherto considered a rare complication of oligodendroglioma. Moreover, we noticed changing patterns of spread in the 1980s. Multiple craniotomies followed by cervical lymph node metastasis characterized the early cases (eg, patient 1). Surgery, radiotherapy, and adjuvant chemotherapy followed by diffuse bony metastasis characterized the recent cases (eg, patients 3, 4, and 10). "Frequent" systemic metastasis may be related to longer survival and changing patterns of spread to aggressive initial treatment. Both can be interpreted as signs of progress in the treatment of anaplastic oligodendroglioma. After all, changing patterns of spread, including distant metastasis, were observed in ovarian cancer with the emergence of effective chemotherapy, aggressive multimodality treatment of the primary tumor, and longer survival.[11] Last, we speculate that metastasis occurred in patients 3 and 10 and perhaps in patient 4 because they received suboptimal early aggressive treatment (Table 1).

Two additional points deserve emphasis. First, we have no data to support the use of chemotherapy for indolent (ie, nonenlarging, nonenhancing, histologically "typical") oligodendroglioma, and second, it is our impression that anaplastic mixed gliomas (ie, oligoastrocytomas) are less sensitive to chemotherapy and have a poorer prognosis.[8]

Anaplastic gliomas are a heterogeneous group of tumors and may differ in their response to cytotoxic drugs. Chemotherapy has had little impact on glioblastoma multiforme, but we are increasingly convinced that anaplastic oligodendroglioma is a chemosensitive tumor. Currently, we are reexamining the predictive value of histologic findings, cautiously pursuing intensive initial treatment for newly diagnosed patients, and modifying our treatments for patients with recurrent oligodendroglioma.

The authors thank their colleagues in the Department of Clinical Neurological Sciences, Leslie Levin, MD, and S. Clifford Sebold, Jr, MD, for helpful discussions, and Pat Gray for preparing the manuscript.

References

1. Macdonald DR, Cascino TL, Schold SC Jr, Cairncross JG. Response criteria for phase II studies of supratentorial malignant glioma. *J Clin Oncol.* In press.

2. Cairncross JG, Macdonald DR. Successful chemotherapy for recurrent malignant oligodendroglioma. *Ann Neurol.* 1988;23:360-364.
3. Levin VA, Edwards MS, Wright DC, et al. Modified procarbazine, CCNU and vincristine (PCV-3) combination chemotherapy in the treatment of malignant brain tumors. *Cancer Treat Rep.* 1980;64:237-241.
4. Levin VA, Silver P, Hannigan J, et al. Superiority of postradiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. *Int J Rad Oncol Biol Phys.* 1990;18:321-324.
5. Macdonald DR, Gaspar LE, Cairncross JG. Successful chemotherapy for newly diagnosed aggressive oligodendroglioma. *Ann Neurol.* 1990; 27:573-574.
6. Cairncross J, Laperriere NJ. Low-grade glioma: to treat or not to treat? *Arch Neurol.* 1989; 46:1238-1239.
7. Brown M, Cairncross JG, Vick NA, et al. Differential response of recurrent oligodendrogliomas vs astrocytomas to intravenous melphalan. *Neurology.* 1990;40(suppl 1):397.
8. Saarinen UM, Pihko H, Makipernaa A. High-dose thiotepa with autologous bone marrow rescue in recurrent malignant oligodendroglioma: a case report. *J Neuro-Oncol.* 1990;9:57-62.
9. Winger MJ, Macdonald DR, Cairncross JG. Supratentorial anaplastic glioma in adults: the prognostic importance of extent of resection and prior low grade glioma. *J Neurosurg.* 1989;71:487-493.
10. Macdonald DR, O'Brien RA, Gilbert JJ, Cairncross JG. Metastatic anaplastic oligodendroglioma. *Neurology.* 1989;39:1593-1596.
11. Dauplat J, Hacker NF, Nieberg RK, Berek JS, Rose TP, Sagae S. Distant metastasis in epithelial ovarian cancer. *Cancer.* 1987;60:1561-1566.

Anaplastic Oligodendrogliomas

Terrence L. Cascino, MD

Over the past 30 years, tremendous effort has been put into discovering effective therapy for primary brain tumor. For the most part, these efforts have concentrated on high-grade gliomas. It has clearly been shown that these tumors are radiosensitive in some cases. There remains great pessimism, though, regarding these tumors, with many patients having little response to chemotherapy at the time of recurrence. This has spurred great interest in novel drugs and new methods of drug delivery to try to increase the effectiveness of chemotherapy.

Cairncross and Macdonald have made the observation that anaplastic oligodendrogliomas may be a subgroup of glioma, which, in fact, is highly chemosensitive. This is an extremely important observation for a number of reasons. If their observations are correct, neuro-oncologists can point to an example of a high-grade glioma whose course can be radically changed by the administration of chemotherapy. Hopefully, this will promote further interest in brain tumor treatments and less pessimism on the part of some physicians and patients. In addition, it is of interest that these dramatic responses were obtained using fairly conventional systemic chemotherapy rather than more toxic approaches.

An appropriate word of warning is voiced in this article, that further studies are needed to delineate the role of intensive PCV (procarbazine, lomustine, and vincristine) therapy in anaplastic oligodendroglioma. In addition, the role of chemotherapy in patients with newly diagnosed tumors must be explored further. Hopefully, the National Cancer Institute of Canada's clinical trial involving multiple centers for phase II study of the use of vincristine in anaplastic oligodendroglioma will further define the treatment of this tumor. In conclusion, Cairncross and Macdonald are to be congratulated for their pioneering work in oligodendroglioma. The results of their multicenter phase II study will be awaited with great anticipation.

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Are Anaplastic Oligodendrogliomas Chemosensitive?

Conventional experience suggests that high-grade gliomas do not respond to chemotherapy. However, Cairncross and Macdonald have found anaplastic oligodendroglioma to be chemoresponsive. Their results are impressive, but their series is small. While questions remain about subtypes, dose, and the best chemotherapeutic combination, it is already clear that at least some anaplastic oligodendrogliomas are chemosensitive.—VLADIMIR HACHINSKI, MD, DSC (MED)

History of Neurology

An Early Description of Slowly Progressive Aphasia

Claudio Luzzatti, MD, Klaus Poeck, MD

• Slowly progressive aphasia without generalized dementia has become an important issue of present-day neuropsychological research. Historically, credit for the first description is usually given to Pick. Another German-speaking author who has published a vivid description of a pertinent case is Pick's contemporary, Max Rosenfeld. This author has also observed a patient with slowly progressive spatial disorientation and visual recognition deficit, and he has discussed these patients in a remarkably modern way in the context of partial atrophy of the brain.

(*Arch Neurol.* 1991;48:228-229)

Mesulam's seminal article on Slowly Progressive Aphasia Without Generalized Dementia[1] has stimulated the interest of researchers working in the field of degenerative cerebral disease. It was recognized that there exists similar cases presenting with progressive language disorder, but also with visual agnosia, spatial deficit, or apraxia.[2-4] The problem whether in the course of the disease process the patients develop other neuropsychological impairment evolving toward generalized dementia or whether the syndrome remains restricted to one cognitive domain is still controversial. Pathologic information is available only for very few cases, and is inconclusive. Therefore, at present, it is not possible to attribute these cases to one of the standard nosological entities of degenerative cerebral disease.

Historically, it is Pick[5-7] who deserves credit for publishing the first descriptions of slowly progressive circumscribed neuropsychological symptoms due to focal brain atrophy. We wish to draw attention to another author, Rosenfeld,[8] who has extensively discussed the problem of partial atrophy of the brain.

Max Rosenfeld was a German neurologist who studied medicine in Königsberg where, at this time, Lichtheim was professor of medicine. He continued his studies in Munich and Strasbourg (Alsace). He became associate professor at Strasbourg University in 1907, where he dedicated himself extensively to studies in the field of physiology and symptomatology of the cerebral hemispheres. Since 1920, he held the chair of Neurology and Psychiatry at Rostock University. Rosenfeld was a contemporary of Wernicke, Isserlin, Kleist, Bonnhoeffer, Alzheimer, Pick, and Goldstein. Yet he does not appear to have worked in close contact with these researchers. This makes the following shrewd clinical observations all the more remarkable.

In an article published in 1909[8] Rosenfeld presented two particularly well-described cases of "partial atrophy of the brain," which he followed up for several years. We report on his patient No. 1 who appears pertinent for the discussion of the status of slowly progressive aphasia.

At the age of 62 years, the patient sought medical advice at the hospital for Nervous Diseases of Strasbourg University. At that time he worked as an insurance agent. He complained of weakness of mentation and stated he had "forgotten about 1000 words." In spite of his complaints he still used to see people in his job. He also frequented coffee shops, played chess, and visited the theater. At times he tended to exhibit a somewhat bizarre behavior that was interpreted by Rosenfeld as indicating loss of intelligence. For instance, he submitted petitions to the local administration requesting that the name of a street be changed or a bridge be constructed.

The patient was well groomed and oriented to time and place. Memory for biographical events was intact, as were reading, spontaneous writing, and writing to dictation, copying, verbal comprehension, spontaneous speech, and repetition. He had no obvious memory problems and did not produce confabulations.

Rosenfeld noted a striking "verbal amnesia" for the names of objects. In a naming task the patient gave the correct name in only seven of about 30 items. In five instances he produced more or less appropriate circumlocutions, eg, glasses: I have had them fixed (showing his own glasses); match box: I always carry these to light something; water pipe: a hole where water comes out; and piece of string: to tie up something.

For four objects he could only indicate the material they are made of. In three instances he produced paraphasic misnamings, eg, pencil for brush; citadel for purse (but he added "I have it in my pocket"); and written document for pen. Naming was not facilitated by tactile or by auditory cuing. The kind of reaction was quite constant. Only rarely was he able to learn the names after repeated testing, eg, watch, matches, lamp, and brush. Rosenfeld noted that the patient remembered from one examination to the next which objects had been shown

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to him before.

Asked to name fruits from memory he ventured only apples and "female apples" (pears). After some hesitation he added small peas, beans, and lentils. The only animal names he produced were dog and horse. Of birds he named only the swallow and called a canary "a small yellow singing bird from Africa, he is my friend."

Summing up, this patient presented with a marked language disorder of anomic type, whereas Rosenfeld did not note other obvious neuropsychological deficits.

Over the following 3 years the patient returned several times to the outpatient clinic, complaining of progressive loss of words. He never had a cardiovascular accident. On repeated examination he again was fully oriented. The prominent aspect was still the severe "verbal amnesia." His spontaneous speech appeared impoverished. Comprehension was intact. Reading and writing were not impaired, but he did not recognize orthographic errors in the text and could not remember the content of a written text. Memory for past events was incomplete with temporal mislocations. Digit span was reduced to four-digit numbers. He could describe pictures even with a latency of some minutes. However, he was unable to repeat short poems and stories or some isolated words. Calculation was still possible for addition, multiplication, and subtraction, but not for division.

One year later he was admitted to the hospital in physically poor shape. He died within a few days at age 66 years.

At autopsy there was no diffuse brain atrophy. However, there was striking atrophy of the left temporal lobe affecting the pole and the second and third temporal gyrus. In contrast, the first temporal gyrus was almost spared. The left sylvian fissure was enlarged. There was considerable reduction of the underlying white matter. The right temporal pole was only slightly atrophic. No ischemic, hemorrhagic, or inflammatory changes were noted on gross inspection or at the microscopic level. The number of glial cells or glial processes was not increased.

The most prominent finding within the atrophic gyri was the reduction of the number of neurons and nerve fibers. The structure of nerve fibers was not altered, neither within nor outside of the cells. The cortical cytoarchitecture was abolished. The number of nerve cells was extremely reduced. A well-preserved fibrillary structure was demonstrated in only a few cells and processes. Most neurons showed rather intact nuclei and perikarya filled with granular material. Many nerve cells were identified by their nucleus only that was surrounded by granular material (Pick bodies?, lipofuscin?, polyglucosan or Lewy bodies?—comment by the authors). The number of satellite cells was not increased. Osmium preparation did not show signs of presumably wallerian degeneration.

Rosenfeld considered this case as a further example of the degenerative "partial atrophy of the left temporal lobe" originally described by Pick.[5] He gave a succinct description of the clinical picture and the course of this disorder: After an initial stage characterized by slow decline of associative and judgment capacities (which might be termed abstract thinking in modern wording), the patients become conspicuous by a mild naming disorder evolving toward a marked amnesic aphasia with the prominent feature of a profound semantic-lexical disorder. Rosenfeld goes on to elaborate that these patients are unable to produce concrete nouns in a given context. At the same time the patients are able to read and repeat these same words even though they may not understand their meaning. In modern terms, they have a profound disruption of verbal semantics, whereas superficial operations are preserved. These symptoms do not occur as the sequelae of an "apoplectic insult" but rather in slow progression. The further course of the language disorder includes semantic paraphasias, comprehension deficit (*Worttaubheit*), and, finally, progressive breakdown of language functions. Rosenfeld also mentions that the patients may develop retrograde and anterograde memory deficit.

In the same article Rosenfeld described a patient with progressive spatial disorientation and visual recognition problems due to bilateral atrophy of the occipital lobe, in particular of the lingual gyrus. He discussed these and other cases[9] in the context of a progressive partial atrophy of the cerebral cortex.

Even though Rosenfeld's article gives a fine early description of a case presenting with slowly progressive aphasia, it does not address the crucial question of presence or absence of dementia in the final stage. The reason is that at the beginning of the century the notion of intelligence was not yet well defined, and embraced in the first place verbal skills that obviously were compromised in these patients. Mesulam[10] maintains that the absence of histologic features specific for Alzheimer's, Pick's, and Creutzfeldt-Jakob's disease is the pathoanatomic finding that permits distinguishing slowly progressive aphasia from other degenerative diseases. Obviously, the older authors did not yet recognize this problem.

References

1. Mesulam M-M. Slowly progressive aphasia without generalized dementia. *Ann Neurol.* 1982;11:592-598.
2. Crystal HA, Horoupian DS, Katzman R, Jotkowitz S. Biopsy-proved Alzheimer disease presenting as a right parietal lobe syndrome. *Ann Neurol.* 1982;12:186-188.
3. Magnani G, Bettoni L, Mazzucchi A. Lesioni atrofiche bioccipitali di incerta natura all'origine di una agnosia visiva. *Riv Neurol.* 1982;52:137-148.
4. De Renzi E. Slowly progressive visual agnosia or apraxia without dementia. *Cortex.* 1986;22:171-180.
5. Pick A. Über die Beziehungen der senilen Hirnatrophie zur Aphasie. *Prager Med Wochenschr.* 1892;17:165-167.
6. Pick A. Zur Symptomatologie der linksseitigen Schläfenlappenatrophie. *Monatsschr Psychiatr Neurol.* 1904;16:378-388.
7. Pick A. Über einen weiteren Symptomenkomplex im Rahmen der Dementia senilis, bedingt durch umschriebene stärkere Hirnatrophie (gemischte Apraxie). *Monatsschr Psychiatr Neurol.* 1906;19:97-108.
8. Rosenfeld M. Die partielle Grosshirnatrophie. *J Psychol Neurol.* 1909;14:115-130.
9. Poeck K, Luzzatti C. Slowly progressive aphasia in three patients. *Brain.* 1988;111:151-168.
10. Mesulam M-M. Primary progressive aphasia: differentiation from Alzheimer's disease. *Ann Neurol.* 1987;22:533-534.

Observations

Anterior Femoral Cutaneous Nerve Injury Following Femoral Artery Reconstructive Surgery

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• Two cases are presented exhibiting symptoms and signs of bilateral anterior femoral cutaneous nerve injury, clinically sparing femoral nerve branches to the saphenous nerve and quadriceps muscles. This occurred following surgical dissection in the femoral triangles associated with femoral artery reconstructive surgery. Anterior femoral cutaneous nerve injury should be considered when anterior medial thigh pain and numbness occur following aortofemoral bypass graft surgery and other types of femoral artery reconstructive surgery.

(*Arch Neurol.* 1991;48:230-232)

Compressive mononeuropathies of the lower limbs related to surgical procedures are well known. They commonly involve the femoral, sciatic, and lateral femoral cutaneous nerves and, more distally, the tibial, peroneal, and saphenous nerves. We describe two cases of postsurgical sensory neuropathy that involved both anterior femoral cutaneous nerves (AFCNs) but clinically spared the rest of both femoral nerve trunks.

REPORT OF CASES

CASE 1.—A 48-year-old man presented with a 3-month history of aching and numbness in the anteromedial aspects of both thighs following bilateral femoral artery bypass graft surgery. Medical history included diabetes mellitus, chronic alcohol abuse, and two femoral artery reconstructive surgeries performed 3 and 4 years earlier. Neurological examination 6 months before the present surgery revealed a distal polyneuropathy without any evidence of femoral nerve dysfunction.

The present bypass surgery was prompted by progressive claudication and rest pain of the right leg and angiographic evidence of occlusion of the right limb of a previously implanted aortobifemoral graft. The procedure was a left-to-right femorofemoral crossover, connecting the left distal limb of the old aortobifemoral graft to the right deep femoral artery. The surgery was uneventful, although the operative report noted abundant scar tissue in the right side of the groin.

Five days after surgery the patient noted burning in both upper knees and an aching pain in both thighs anteromedially, followed a few days later by a dead, raw feeling in the same distribution. There was no difficulty walking, climbing stairs, or extending either knee. During the ensuing 3 months, burning around the knees and soreness-numbness of the anteromedial aspect of the thighs persisted. Symptoms increased with sitting or lying and were unaffected by walking.

Neurological examination 3 months after surgery revealed absent pin and cold sensation in a well-defined area of both thighs anteromedially, extending from 10 cm below the inguinal creases to just below both patellae (Figure, left). In addition, in the lower limbs there was a distal loss to pin, cold, and vibratory sensation bilaterally, although sensation was preserved in most of the saphenous nerve distribution. Strength and bulk of the lower limb muscles, including the quadriceps bilaterally, were normal. Deep tendon reflexes were brisk in both knees but absent in the ankles.

Standard motor and sensory nerve conduction studies (Table) were consistent with an axonal loss sensorimotor polyneuropathy. Motor conduction studies of both femoral nerves revealed normal latencies and amplitudes of the compound muscle action potentials. Needle electromyography (EMG) of both vastus medialis muscles was normal, with no signs of denervation or chronic neuropathy.

Carbamazepine was prescribed, with resultant improvement in the burning sensation. Neurological evaluation 1 year after surgery revealed patchy, less well-defined areas of diminished pin and cold sensation over both anteromedial thighs with some residual burning in those regions.

CASE 2.—A 72-year-old man presented with a 5-month history of medial right thigh pain and numbness following bilateral aortofemoral bypass surgery. Medical history included mild renal failure, rheumatoid arthritis of the knees, and recurrent leg phlebitis treated with oral warfarin sodium. During evaluation for the phlebitis, a computed tomographic scan revealed an aneurysm of the infrarenal abdominal aorta with extension into both common iliac arteries.

The aneurysm was surgically repaired with placement of bilateral aortofemoral bypass grafts. After surgery, the patient noticed a numb, dead sensation in the upper half of both thighs anteromedially, followed a week later by a persistent pain in the anterior right thigh. The numbness in the left leg improved considerably by 6 weeks after surgery. There were never any complaints of leg or thigh weakness. Computed tomography of the pelvis and abdomen 6 weeks after surgery showed no evidence of hematoma or mass lesion.

Neurological examination 5 months after surgery revealed decreased pin and cold sensation limited to an oval region involving both thighs anteromedially (right more than left), extending just below the inguinal ligament to about 10 cm above the knee (Figure, right). There was hyperesthesia over the anterior right thigh between the inguinal ligament and the knee. Strength and bulk of lower limb muscles, including the quadriceps bilaterally, were normal. Deep tendon reflexes were diminished in the right knee, normal in the left knee, and absent in both ankles.

Nerve conduction studies of the lower

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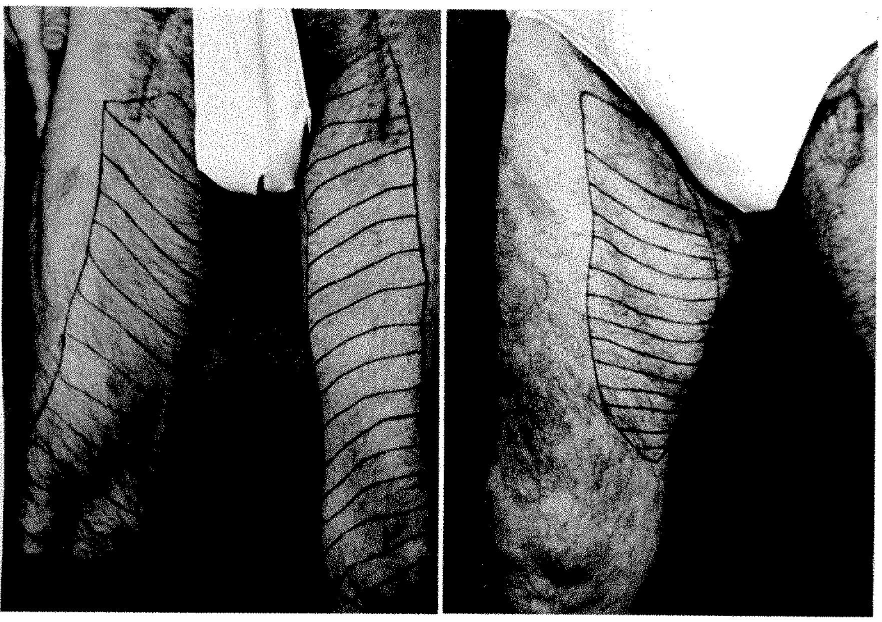

Striped regions indicate areas of decreased pin and cold sensation in distribution of anterior femoral cutaneous nerve. Left, Case 1. Right, Case 2.

Nerve Conduction Studies*

	Case 1			Case 2		
Nerve	TL, ms	Amp	CV, m/s	TL, ms	Amp, mV or μV	CV, m/s
R/L femoral (motor)†	6.5/6.6	4.0/4.0 mV	. . .	5.8/5.5	4.0/5.0	. . .
R peroneal (motor)	6.5	0.35 mV	47	5.2	9.0	43
R tibial (motor)	4.1	0.45 mV	40	3.9	9.0	35
R median (motor)	4.9	12.0 mV	45	. . .	. . .	. . .
R ulnar (motor)	2.7	11.0 mV	47	. . .	. . .	. . .
R median (sensory)	3.2	10 μV	47	. . .	. . .	. . .
R ulnar (sensory)	2.9	8 μV	45	. . .	. . .	. . .

*TL indicates terminal latency; Amp, amplitude; and CV, conduction velocity. There was no response in the right sural nerve for case 2.

†Stimulated at inguinal ligament, recorded at vastus medialis (distance, 28.5 cm, case 1; 30.0 cm, case 2).

limbs (Table) suggested a sensory polyneuropathy. Motor conduction studies of both femoral nerves revealed normal latencies and amplitudes. Needle EMG of the lower limbs revealed positive sharp waves at rest in the right vastus lateralis and an increase in long-duration polyphasic motor unit action potentials in the right vastus lateralis, right tibialis anterior, and right gastrocnemius muscles. Left and right vastus medialis and left vastus lateralis muscles were normal.

Follow-up examination 6 months after surgery showed complete resolution of the right anterior thigh pain with lessening of the bilateral sensory deficit in the thighs; 1 year after surgery, sensory and motor examination results of the lower limbs were normal.

COMMENT

Both patients suffered nerve injuries largely restricted to the AFCNs. The clinical syndrome of AFCN injury consists of numbness and aching pain in the thigh anteromedially, sometimes associated with a burning sensation in the knee, with no difficulty in walking or extending the knee. Cutaneous sensation is diminished or absent in the distribution of the AFCN but present in the distribution of the saphenous nerve, and motor examination, particularly of quadriceps strength, shows no abnormality. Both patients, in addition, had clinical and EMG evidence of a distal sensorimotor polyneuropathy, which may have made them more susceptible to isolated nerve injury. The subclinical neuropathic findings on right quadriceps EMG in case 2 suggest that, in this patient, mild injury to the right main femoral nerve trunk may have accompanied injury to the AFCN.

The anatomy of the femoral nerve and its AFCN branches may help to explain the precise localization of our patients' lesions. The femoral nerve, formed from the second, third, and fourth lumbar nerves, descends within the abdomen and passes behind the inguinal ligament into the thigh. In the proximal femoral triangle, the nerve divides into an anterior and a posterior division, both of which divide almost immediately into their respective branches.

The AFCN consists of cutaneous branches that arise from the anterior division of the femoral nerve. Lateral cutaneous branches of the AFCN (also known as the intermediate femoral cutaneous nerve) supply the anterior surface of the thigh as far distal as the knee, while medial cutaneous branches (also known as the medial femoral cutaneous nerve) supply the adjacent medial surface of the thigh.[1(pp759-762)-3] The anterior division of the femoral nerve also supplies muscular branches to the sartorius. The posterior division of the femoral nerve supplies the saphenous nerve and muscular branches to the quadriceps.

The most likely cause of the bilateral sensory mononeuropathy in our two patients was trauma from surgical dissection or retraction of the AFCN branches as they cross from a lateral to medial direction anterior to the common femoral artery bifurcation in the femoral triangle.[1(pp896-897),2] An alternative possibility is that trauma was limited to the anterior division of the femoral nerve in its position in the proximal femoral triangle, just lateral to the common femoral artery. Either possibility would explain the selective damage to AFCN branches while branches to the saphenous nerve and quadriceps muscles were clinically spared.

The clinical presentation of AFCN injury should not be confused with several other entities. Postoperative pain, burning, and numbness of the thigh in a patient with established peripheral vascular disease may suggest to the clinician a diagnosis of recurrent arterial vascular insufficiency, thrombophlebitis, or high lumbar (L-2 to L-4) radiculopathy. A careful neurological and medical evaluation, with particular attention to the cutaneous distribution of the AFCN, should help to clarify the diagnosis.

Isolated neuropathy of the AFCN without clinical involvement of the main femoral nerve trunk, although rarely reported[4,5] may not be an uncommon complication of peripheral vascular surgery. Based on our experience with two surgical cases, it seems that AFCN injury can have a relatively benign course with gradual resolution of symptoms and signs. Awareness of this entity, along with proper attention to meticulous surgical technique, may help prevent such a complication. In the setting of thigh pain and numbness following aortofemoral artery bypass and other femoral artery reconstructive surgery, AFCN injury should always be considered.

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References

1. Romanes GJ. *Cunningham's Textbook of Anatomy.* 11th ed. New York, NY: Oxford University Press Inc., 1972:759-762, 896-897.
2. Sunderland S. *Nerves and Nerve Injuries.* 2nd ed. New York, NY: Churchill Livingstone Inc., 1978:999-1006.
3. Williams PL, Warwick R, Dyson M, Bannister LH, eds. *Gray's Anatomy.* 37th ed. New York, NY: Churchill Livingstone Inc., 1989:1143.
4. Shaw PJ, Bates D, Cartlidge NEF, et al. Neurologic and neuropsychological morbidity following major surgery: comparison of coronary artery bypass and peripheral vascular surgery. *Stroke.* 1987;18:700-707.
5. Dawson DM, Hallett M, Millender LH. *Entrapment Neuropathies.* Boston, Mass: Little Brown & Co Inc., 1983:233.

Frontal Impairment and Hypoperfusion in Neuroacanthocytosis

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• Cerebral blood flow tomography, by xenon 133 inhalation or HMPAO (^{99}mTc-*d*, *l*-hexamethyl-propylene amine oxime) technetium Tc 99m injection, revealed a severe hypoperfusion in both frontal lobes of a 40-year-old woman with confirmed neuroacanthocytosis. This finding occurred in conjunction with neuropsychological deficits consistent with selective frontal lobe dysfunction. This observation is the first documentation of this type of dementia in neuroacanthocytosis.

(*Arch Neurol.* 1991;48:232-234)

The differential diagnosis of vocal tics and choreic movements in the adult includes Huntington's disease, Gilles de la Tourette syndrome of late onset, and neuroacanthocytosis (NA).[1] Classically, acanthocytosis in the peripheral blood, an elevated creatine kinase level, and a normal lipoproteinemia concentration are characteristic of the NA syndrome.[2] Conversely, the neuroimaging findings in NA are described as similar to those of Huntington's disease, with caudate atrophy on computed tomographic scan and caudate hypometabolism[3,4] on positron emission tomography. We describe a case of a 40-year-old woman with NA (at first incorrectly diagnosed as Huntington's disease or late-onset Tourette syndrome) in whom single-photon emission tomography revealed a cerebral blood flow pattern of severe, isolated flow decrease in both frontal lobes, with little or no perfusional abnormalities in the caudate nuclei. Neuropsychological testing disclosed isolated frontal lobe dysfunction, a clinical pattern unlike those usually found in NA.[5,6]

REPORT OF A CASE

A 40-year-old woman, with no relevant personal or family history, was admitted for disabling abnormal and progressively worsening movements of 6 years' duration. The movements consisted of involuntary orofacial and tongue contractions with snorting, grunting, humming, lip smacking, and tongue clicks, as well as truncal dystonia and choreic movements of all four limbs. These involuntary movements were unrelieved by either benzodiazepines or tetrabenazine. Two years before admission, a progressive, hyperkinetic dysarthria began with the most salient speech dysfunctions being rate variability, irregular articulatory breakdown, hypernasality, occasional stuttering, and palilalia. One year before admission, generalized seizures developed, which responded to treatment with carbamazepine. There was no dysphagia, propulsive eating dystonia, or oral self mutilation.

Neuropsychological examination revealed a cooperative right-handed woman, well aware of her difficulties. There were no psychiatric manifestations and the Beck Depression Inventory proved that there was no concomitant depression. The patient's verbal and performance intelligence quotient scores were 102 and 75, values lower than expected given her level of academic achievement. The Wechsler memory scale revealed a lowered quotient at 86, with the patient's verbal learning capacity being superior to her nonverbal learning capacity. There was an inability to inhibit intrusion in interference conditions during the Stroop test (part C: colored color names, 69 seconds), as well as an inability to inhibit immediate response tendencies on the Alternating Sequence Test, and to achieve more than one category on the Wisconsin Card Sorting Test (20 perseverative errors, or 83%). She also had difficulties with "go-no-go" (excessive errors of commission on the no-go trials with both hands). Luria's numerical word problems could not be resolved though basic calculations were intact. Results of Rey's Auditory Verbal Learning Test were within normal limits. There were no word finding difficulties. Verbal fluency (names of animals and words beginning with P, F, and L in a one-minute time span) was preserved.

Cerebral computed tomographic scan showed a slight bilateral atrophy of the caudate nucleus (Fig 1). Nerve conduction velocities were normal, and electromyographic examination of the limbs disclosed no abnormalities. Microscopic examination of fresh serum revealed the presence of numerous acanthocytes (up to 30%), with a creatine kinase elevation and a normal lipoproteinemia concentration.

Quantified cerebral blood flow determination was performed by the xenon 133 inhalation method, and a rapidly rotating single-photon emission computed tomograph (Tomomatic 564 single-photon emission computed tomograph, Medimatic, Copenhagen, Denmark) developed by Lassen and Stokely. This method has been described in detail elsewhere.[7] Mean global cerebral blood flow and mean regional cerebral blood flow were calculated within six standardized paired regions of interest depicting the main vascular territories, as defined by Rootwelt and coworkers[8] (color

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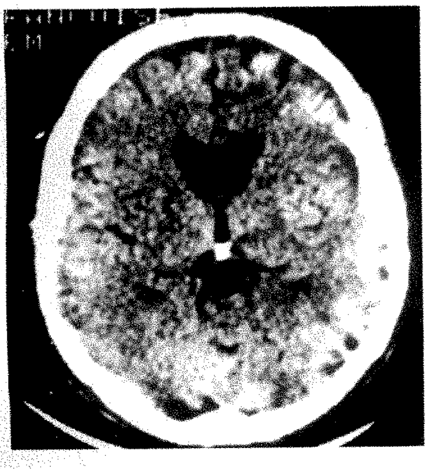
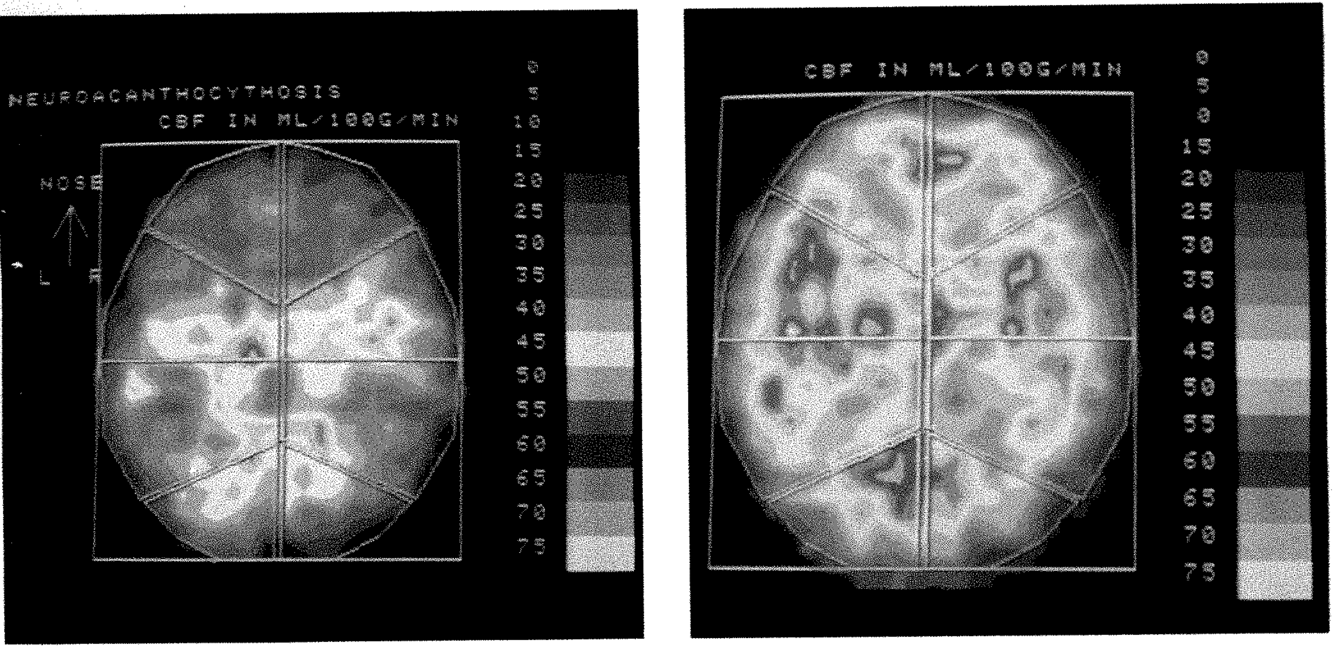


Fig 1.—The patient's cerebral computed tomographic scan showed a slight atrophy of the caudate nuclei.

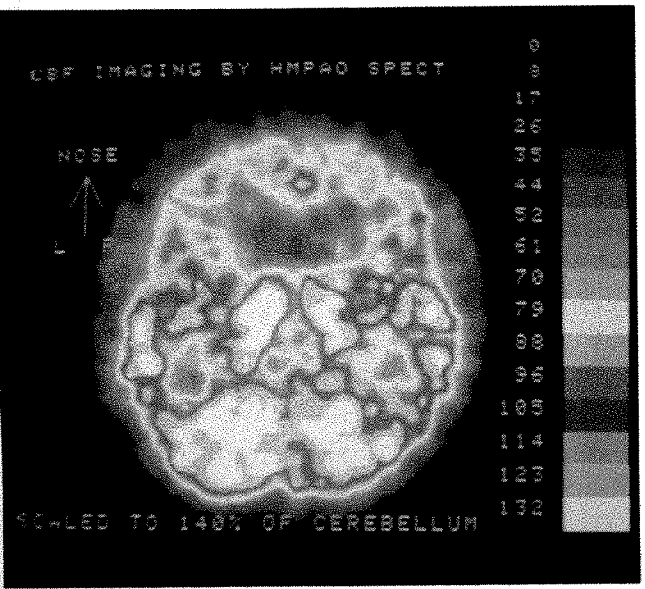
Mean Cerebral Blood Flow of the Patient and of 35 Control Subjects

Population	Age, y (Mean ± 1SD)	Global Cerebral Blood Flow mL/100 g per Minute (Mean ± 1 SEM)	Frontal Cerebral Blood Flow mL/100 g per Minute (Mean ± 1 SEM)
Present case	40.0	40.5	32.5
Control subjects (n = 35)	41.8 ± 2.2	50.9 ± 1.2	48.1 ± 1.1



Color Fig 1. Left, The patient's xenon 133 cerebral blood flow pattern, 5 cm above the orbitomeatal line showed a severe flow decrease in the frontal lobes. An arrow shows the slice orientation.

Right, The cerebral blood flow pattern of a normal control subject at the same level is included for comparison. At the extreme right of both flow maps is the cerebral blood flow scale, in milliliters per 100 g per minute, showing the identical scaling.



Color Fig 2.—The patient's HMPAO cerebral blood flow pattern, on the same slice as in color Fig 1, showing both the severe frontal hypoperfusion and the slight flow decrease in the caudate nuclei. The image is linearized according to Yonekura and coworker's technique,[9] and scaled to 140% of the cerebellum.

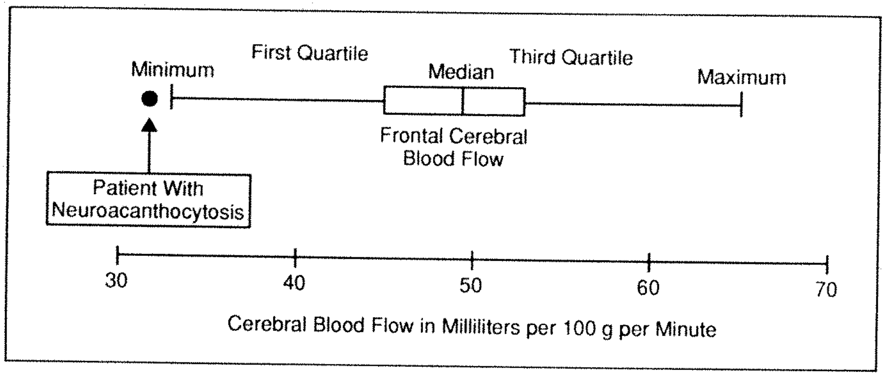


Fig 2.—A "box-and-whisker" plot of frontal flows in a normal population of 35 right-handed females. The patient's values are well outside the first percentile, as indicated by the arrow.

Fig 1), and applied to the third tomographic slice (located 5 cm above the orbitomeatal line). The quantitative xenon 133 cerebral blood flow measurements thus obtained in this case are depicted in the Table, compared with the same averaged results ± 1 SEM obtained in a control population of similar mean age, consisting of 35 normal, right-handed females. A "box-and-whisker plot" of the frontal flows (Fig 2) shows that our patient's frontal lobe values were well outside the normal range.

In order to better evaluate the flows in the caudate nuclei, another single-photon emission tomographic study was performed using the same equipment and a high-resolution collimator, after the intravenous administration of the new cerebral blood flow tracer HMPAO (^{99}mTc-*d,l*-hexamethylpropylene amine oxime). This tracer allows cerebral blood flow imaging of higher resolution than xenon 133, though absolute quantification is not routinely possible because of its long biological half-life. High-resolution cerebral blood flow imaging by HMPAO, using Yonekura[9] and Lassen's[7] "linearization technique," confirmed the existence of severe frontal hypoperfusion and revealed a slight decrease in the caudate nuclei (color Fig 2).

COMMENT

The neuropsychological pattern of NA has rarely been studied, and is still far from completely understood, as mental alterations are not usually a conspicuous feature of this disease.[5] When mental alterations do exist, the patterns so far described range from mild personality changes with slight intellectual impairment[10] to a "Huntington's disease-like" pattern with mild dementia, visuopraxic problems, anomia, and a retrieval deficit for verbal and nonverbal material.[6] Our observation adds another facet to the possible intellectual deficits in NA: that of predominantly frontal dysfunction, as witnessed by multiple perseverative errors, an excessive vulnerability to external intrusion, an inability to inhibit immediate but inappropriate responses, and an incapacity in initiating concepts.

These mental alterations were reflected in the perfusional abnormalities of this patient, a cerebral blood flow pattern quite different from that previously described in NA, Huntington's disease, or Tourette syndrome.[2-4] Both xenon 133 and HMPAO single-photon emission tomography revealed a severe focal flow decrease in both frontal lobes, with only a slight decrease in the caudate nuclei. Xenon 133 single-photon emission tomography also showed a slight global flow decrease. In contrast, the cerebral blood flow pattern in Huntington's disease is limited to a flow reduction in the caudate nuclei[4] while severe frontal lobe abnormalities are not seen in Tourette syndrome. This frontal lobe hypoperfusion is similar to that seen in the so-called "dementia of frontal lobe type," a clinical and cerebral blood flow entity, whose various pathogeneses include Pick's disease, Parkinson's disease, supranuclear palsy, and frontal lobe degeneration.[11,12] It is then ascribed to a specific degenerative process of the frontal lobes.[12] However, such a process has never been pathologically described in NA,[6] and the computed tomographic scan in this case showed no sign of frontal atrophy. Another possible cause of this frontal hypoperfusion would be a form of intrahemispheric diaschisis, similar to that described in the lesions of the thalamus[13] or the internal capsule,[14] and attributed to cortical deafferentation.[13]

Cerebral blood flow tomography would thus seem to be a very useful tool, not only in the differential diagnosis of diseases of the basal ganglia, such as Huntington's disease, Tourette syndrome, and neuroacanthocytosis, but also in the understanding of the physiological repercussions of the pathological processes involved.

References

1. Tolosa E, Pena J. Involuntary vocalizations in movement disorders. In: Jankovic J, Tolosa E, eds. *Facial Dyskinesias.* New York, NY: Raven Press; 1988;49:343-363.

2. De Yebenes JG, Brin M, Mena MA, et al. Neurochemical findings in neuroacanthocytosis. *Movement Disord.* 1988;3:300-312.

3. Kuhl DE, Phelps ME, Markham CH. Cerebral metabolism and atrophy in Huntington's disease determined by 18 FDG and computed tomographic scan. *Ann Neurol.* 1982;12:425-434.

4. Starkstein S, Brandt J, Folstein S, et al. Neuropsychological and neuroradiological correlates in Huntington's disease. *J Neurol Neurosurg Psychiatry.* 1988;51:1259-1263.

5. Medalia A, Merriam A, Sandberg M. Neuropsychological deficits in choreoacanthocytosis. *Arch Neurol.* 1989;46:573-575.

6. Bharucha EP, Bharucha NE. Choreo-acanthocytosis. *J Neurol Sci.* 1989;89:135-139.

7. Lassen N, Rommer P. Cerebral blood flow tomography by single photon emission computerized tomography using ^{133}Xe in cerebrovascular disease. In: Ventura A, Crepaldi G, Senin U, eds. Basel, Switzerland: S Karger AG; 1986;14:71-82.

8. Rootwelt K, Dybevold S, Nyberg-Hansen R, Russel D. Measurement of cerebral blood flow with ^{133}Xe inhalation and dynamic single photon emission computer tomography: normal values. *Scand J Clin Lab Invest.* 1986;46(suppl 184):97-105.

9. Yonekura Y, Nishizawa S, Mukai T, et al. SPECT with ^{99m}Tc-*d,l*-hexamethyl-propylene amine oxime (HMPAO) compared with regional cerebral blood flow measured by PET: effects of linearization. *J Cereb Blood Flow Metab.* 1988; 8:82-89.

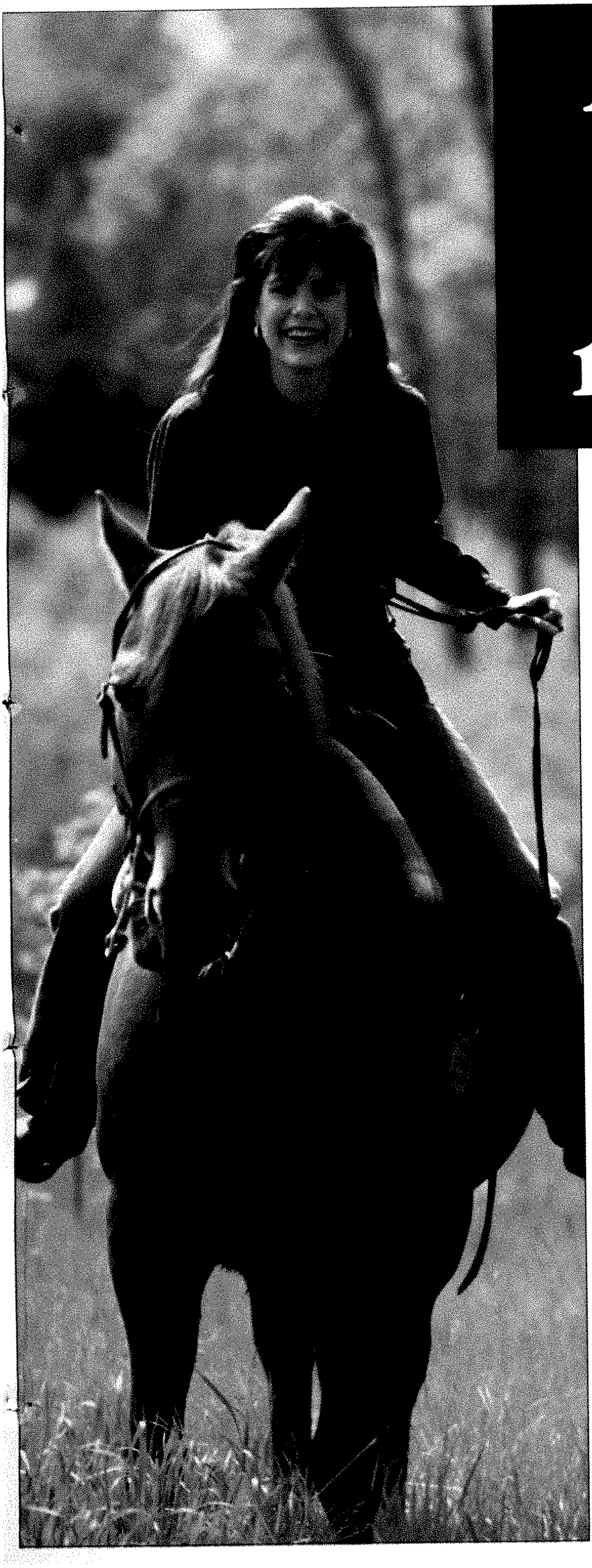
10. Weintraub S, Mesulam MM. Mental state assessment of young and elderly adults in behavioral neurology. In: Mesulam MM, ed. *Principles of Behavioral Neurology.* Philadelphia, Pa: Davis; 1985:71-123.

11. Neary D, Snowden JS, Northen B, Goulding P. Dementia of frontal lobe type. *J Neurol Neurosurg Psychiatry.* 1988;51:353-361.

12. Brun A. Frontal lobe degeneration of non-Alzheimer type, I: neuropathology. *Arch Gerontol Geriatr.* 1987;6:193-208.

13. Baron JC, D'Antona R, Pantano P, Serdaru M, Samsun Y, Bousser MG. Effects of thalamic stroke on energy metabolism of the cerebral cortex. *Brain.* 1986;109:1243-1259.

14. Pappata S, Baron JC, Cambon H, et al. Remote effects of internal capsular infarcts: a positron tomography study. In: Meyer JS, ed. *Cerebral vascular disease.* New York, NY: Elsevier; 1987:211-217.



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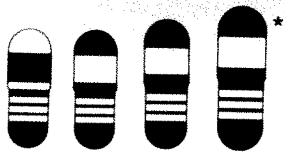

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BRIEF SUMMARY *(FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE CIRCULAR.)*

INDERAL® LA brand of propranolol hydrochloride **(Long Acting Capsules)**

DESCRIPTION. INDERAL LA is formulated to provide a sustained release of propranolol hydrochloride. INDERAL LA is available as 60 mg, 80 mg, 120 mg, and 160 mg capsules.

CLINICAL PHARMACOLOGY. INDERAL is a nonselective, beta-adrenergic receptor-blocking agent possessing no other autonomic nervous system activity. It specifically competes with beta-adrenergic receptor-stimulating agents for available receptor sites. When access to beta-receptor sites is blocked by INDERAL, the chronotropic, inotropic, and vasodilator responses to beta-adrenergic stimulation are decreased proportionately.

INDERAL LA Capsules (60, 80, 120, and 160 mg) release propranolol HCl at a controlled and predictable rate. Peak blood levels following dosing with INDERAL LA occur at about 6 hours, and the apparent plasma half-life is about 10 hours. When measured at steady state over a 24-hour period the areas under the propranolol plasma concentration-time curve (AUCs) for the capsules are approximately 60% to 65% of the AUCs for a comparable divided daily dose of INDERAL Tablets. The lower AUCs for the capsules are due to greater hepatic metabolism of propranolol, resulting from the slower rate of absorption of propranolol. Over a twenty-four (24) hour period, blood levels are fairly constant for about twelve (12) hours, then decline exponentially.

INDERAL LA should not be considered a simple mg-for-mg substitute for conventional propranolol and the blood levels achieved do not match (are lower than) those of two to four times daily dosing with the same dose. When changing to INDERAL LA from conventional propranolol, a possible need for retitration upwards should be considered, especially to maintain effectiveness at the end of the dosing interval. In most clinical settings, however, such as hypertension or angina where there is little correlation between plasma levels and clinical effect, INDERAL LA has been therapeutically equivalent to the same mg dose of conventional INDERAL as assessed by 24-hour effects on blood pressure and on 24-hour exercise responses of heart rate, systolic pressure, and rate pressure product. INDERAL LA can provide effective beta blockade for a 24-hour period.

INDICATIONS AND USAGE. Hypertension: INDERAL LA is indicated in the management of hypertension; it may be used alone or used in combination with other antihypertensive agents, particularly a thiazide diuretic. INDERAL LA is not indicated in the management of hypertensive emergencies.

Angina Pectoris Due to Coronary Atherosclerosis: INDERAL LA is indicated for the long-term management of patients with angina pectoris.

Migraine: INDERAL LA is indicated for the prophylaxis of common migraine headache. The efficacy of propranolol in the treatment of a migraine attack that has started has not been established and propranolol is not indicated for such use.

Hypertrophic Subaortic Stenosis: INDERAL LA is useful in the management of hypertrophic subaortic stenosis, especially for treatment of exertional or other stress-induced angina,, palpitations, and syncope. INDERAL LA also improves exercise performance. The effectiveness of propranolol hydrochloride in this disease appears to be due to a reduction of the elevated outflow pressure gradient, which is exacerbated by beta-receptor stimulation. Clinical improvement may be temporary.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

> IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema)—PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted, however, that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Beta blockers should be used with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia, but other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism. Therefore, abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, the tachycardia was replaced by a severe bradycardia requiring a demand pacemaker. In one case, this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Propranolol should be used with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL (propranolol HCl) is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity which may result in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, for both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.
Ethanol slows the rate of absorption of propranolol.
Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.
Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.
Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.
Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.
Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.
Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: Long-term studies in animals have been conducted to evaluate toxic effects and carcinogenic potential. In 18-month studies, in both rats and mice, employing doses up to 150 mg/kg/day, there was no evidence of significant drug-induced toxicity. There were no drug-related tumorigenic effects at any of the dosage levels. Reproductive studies in animals did not show any impairment of fertility that was attributable to the drug.

PREGNANCY: Pregnancy Category C: INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose.

There are no adequate and well-controlled studies in pregnant women. INDERAL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Caution should be exercised when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. Oculomucocutaneous reactions involving the skin, serous membranes, and conjunctivae reported for a beta blocker (practolol) have not been associated with propranolol.

DOSAGE AND ADMINISTRATION: INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

HYPERTENSION—*Dosage must be individualized.* The usual initial dosage is 80 mg INDERAL LA once daily, whether used alone or added to a diuretic. The dosage may be increased to 120 mg once daily or higher until adequate blood pressure control is achieved. The usual maintenance dosage is 120 to 160 mg once daily. In some instances a dosage of 640 mg may be required. The time needed for full hypertensive response to a given dosage is variable and may range from a few days to several weeks.

ANGINA PECTORIS—*Dosage must be individualized.* Starting with 80 mg INDERAL LA once daily, dosage should be gradually increased at three- to seven-day intervals until optimal response is obtained. Although individual patients may respond at any dosage level, the average optimal dosage appears to be 160 mg once daily. In angina pectoris, the value and safety of dosage exceeding 320 mg per day have not been established.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

MIGRAINE—*Dosage must be individualized.* The initial oral dose is 80 mg INDERAL LA once daily. The usual effective dose range is 160-240 mg once daily. The dosage may be increased gradually to achieve optimal migraine prophylaxis. If a satisfactory response is not obtained within four to six weeks after reaching the maximal dose, INDERAL LA therapy should be discontinued. It may be advisable to withdraw the drug gradually over a period of several weeks.

HYPERTROPHIC SUBAORTIC STENOSIS—80-160 mg INDERAL LA once daily.

PEDIATRIC DOSAGE—At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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BC/BE NEUROLOGIST to join busy neurology practice in southeast Virginia, South Hampton Roads area, near Norfolk, Williamsburg and Outer Banks. University affiliation available. EMG and sleep training desirable. Competitive salary leading to partnership. Send CV to: Southeastern Neurology Group, Robert Hansen, MD, 1890 North Main Street, Suite G01, Suffolk, VA 23434.

CENTRAL OHIO—BC/BE neurologist to join busy solo practice located near Columbus. Experience in EMG, EEG and EP is desirable. Attractive compensation and benefits with productivity bonus. Full partnership in two years. Reply to: Robert M. Taylor, MD, 66 McMillen Drive, Newark, OH 43055. Or call: (614) 344-6992.

CHARLOTTE, NORTH CAROLINA: High quality group of six neurologists, all of whom are subspecialized, seeks to add a well-trained specialist. Contact: Mike Kaufman, MD, 126 Cottage Place, Charlotte, NC 28207. Or call: (704) 334-7311.

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PEDIATRIC NEUROLOGY—Premier group in medium-sized community in the northern midwest seeking BC/BP pediatric neurologist to join two adult practitioners. Practice in place. Excellent financial package available leading to partnership. Phone or write: Mary Frances Lyons, MD, at (800) 678-7858 (local (314) 726-1603), c/o Cejka & Company, 222 South Central, Suite 400, St. Louis, MO 63105. FAX # (314) 726-0026.

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CHICAGO SUBURBAN solo practitioner with a busy practice seeking a full-time BC/BE clinical neurologist. EMG skills required. Immediate opening. Wonderful opportunity to expand with possible early partnership. Reply with CV to: Yvonne Jurcik, MD, 125 East Lake Cook Road, Buffalo Grove, IL 60089.

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The Ochsner Clinic in New Orleans is seeking a general neurologist to join the department. The individual should be board-certified or board-eligible in neurology.

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Please send curriculum vitae to:
Dr. Richard Strub
Chairman, Department of Neurology
Ochsner Clinic
1514 Jefferson Highway
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Fellowships

PAIN FELLOWSHIP. The Pain Service in the Department of Neurology at Memorial Sloan-Kettering Cancer Center is seeking a board-eligible/board-certified neurologist for a pain fellowship. This is a one- or two-year position that offers comprehensive training in pain evaluation and treatment, with a strong emphasis on cancer pain. Fellows will participate in clinical investigations of neuro-oncologic pain syndromes and the pharmacology of opioid analgesics. Laboratory research opportunities directed at the mechanisms of opiate action and the molecular pharmacology of opiate receptors are also available. Please contact: K.M. Foley, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

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If interested contact:
Randy Wellman, Office Manager
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The Department of Neurology,
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is recruiting a

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The Department of Neurology, a rapidly expanding 26-member academic group practice with an accredited neurology residency training program at Henry Ford Hospital & Health Sciences Center, is seeking additional BC/BE neurologists with the following subspecialty interests:

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(6) cerebrovascular diseases.

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Fellowships

FELLOWSHIP in Cerebrovascular Disease: Fellowships in cerebrovascular disease are available in the Department of Neurology at the University of Iowa. Comprehensive clinical training in management of patients with stroke is complemented by opportunities for clinical or basic research. Fellows are active participants in patient care and collaborate in several on-going local and multi-center clinical research studies. Candidates should be board-eligible or -certified in neurology and be licensed to practice medicine in the United States. Please send inquiries to either Harold P. Adams, Jr., MD, or Jose Biller, MD, Division of Cerebrovascular Diseases, Department of Neurology, University of Iowa, Iowa City, IA 52242. Or call: (319) 356-4110. The University of Iowa is an affirmative action/equal opportunity employer. Women, minorities and handicapped are encouraged to apply.

EPILEPSY FELLOWSHIP—Immediate opening available for one or two year epxerience. Active clinical program with emphasis on comprehensive medical and psychosocial management and clinical drug trials. Intermediate level epilepsy monitoring (video and ambulatory EEG) is in place. Training in EEG, EP, quantified EEG and brain mapping is available. Interested applicants may apply to: Dr. Venkat Ramani, Department of Neurology, Albany Medical College, Albany, NY 12208. (518) 445-5227.

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The Departments of Ophthalmology and Neurology, University of Michigan. Position for one year period, July 7, 1992 to July 6, 1993. Trainee appointed as a lecturer with stipend and fringe benefits. Inquiries (before June 1, 1991) to: Jonathan D. Trobe, MD,

W K Kellogg Eye Center
1000 Wall Street, Ann Arbor, MI 48105
The University of Michigan
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EMG AND NEUROMUSCULAR Disease Fellowship, University of Mississippi Medical Center. Comprehensive fellowship in clinical neuromuscular disease, electromyography (including single fiber EMG), and muscle and nerve pathology for one or two years. The experience is based on a large MDA clinic (over 500 patients), an active EMG laboratory (700 procedures/year), and a muscle pathology laboratory within the department of neurology. Optional time in a basic science laboratory studying calcium and receptor mechanism in neuromuscular disease. Send CV and three letters of recommendation to: S.H. Subramony, MD, Department of Neurology, University of Mississippi Medical Center, 2500 North State Street, Jackson, MS 39216-4505. Equal opportunity employer, M/F/H/V.

GERIATRIC NEUROLOGY FELLOWSHIP. A two-year fellowship is available in geriatric neurology, beginning July 1, 1991. This VA-supported fellowship provides multi-disciplinary training in geriatric neurology with formal rotations on the 17-bed Geriatric Evaluation and Management Service at the Portland VA Medical Center. Fellows will also participate in clinical and research activities of the Alzheimer's Disease Center of Oregon and the Oregon Brain Aging Study at both the VA Medical Center and Oregon Health Sciences University. Emphasis will be placed on the design and implementation of independent research protocols. A broad range of research opportunities are available and include such topics a quantitative image analysis, the neuropharmacology of movement disorders, cerebrovascular disease in the elderly, and the neurology, neuropsychology and neuropathology of the very old. Applicants must be board-eligible or -certified in neurology. To apply, send CV and two letters of recommendation to: Jeffrey Kaye, MD, Director, Geriatric Neurology, Portland VA Medical Center, 3710 SW U.S. Veterans Hospital Road, P.O. Box 1034, Portland, OR 97207. Telephone: (503) 273-5171 or (503) 494-7772. The Department of Veterans Affairs and the Oregon Health Sciences University are equal opportunity employers.

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Fellowships

THE DEPARTMENT OF NEUROLOGY, University of Louisville has an opening for Clinical Neurophysiology Fellowship for 1991-92. Candidate will have the options to combine EEG with EMG or evoked potentials or clinical polysomnography. Interested applicants should forward their curriculum vitae to: Vasudeva Iyer, MD, Department of Neurology, University of Louisville, Louisville, KY 40292. (502) 588-7981.

NEURO-ONCOLOGY fellowship/instructorships are available for July 1991 and 1992. The University of California, San Francisco, Department of Neurological Surgery, Neuro-oncology Service, offers unprecedented opportunities to participate in chemotherapy and radiation therapy trials of children and adults with brain tumors. Practice is primarily outpatient; some 2,000 patient visits each year. An optional second year of laboratory research is available. Applicants for this position must possess a California medical license and be board-eligible or board-certified in neurology, neurosurgery, or medical oncology. There are two positions available. Apply to: Michael Prados, MD, University of California, Department of Neurological Surgery, Neuro-oncology Service, ACC-841, San Francisco, CA 94143-0372. The University of California is an equal opportunity/affirmative action employer. Women and minorities are encouraged to apply.

NEUROEPIDEMIOLOGY training fellowship available for board-eligible neurologist beginning July 1, 1991 at the Sergievsky Center and Neurological Institute, Columbia-Presbyterian Medical Center. Opportunity to earn a MS or MPH in epidemiology and work on ongoing clinical studies. Special interest in epilepsy or cerebrovascular disease preferred. Address inquiries to: Dr. W. Allen Hauser, Neuro-epidemiology Training Program, Sergievsky Center, 60 Haven Avenue, New York, NY 10032. Columbia University is an equal opportunity/affirmative action employer.

AGING AND DEMENTIA/BEHAVIORAL neurology clinical research fellowship available for board-eligible or -certified neurologist, July 1, 1991, at the Department of Neurology, Columbia Presbyterian Medical Center. Unexpected opening. Bi-lingual (Spanish) physician preferred. Address inquiries to: Dr. Richard Mayeux, Neurological Institute, 710 West 168th Street, New York, NY 10032. Columbia University is an equal opportunity employer.

Residencies

THE UNIVERSITY OF CHICAGO Neurology Department is offering a second year neurology residency position (PGY 3) beginning July 1991. For information contact: Richard P. Kraig, PhD, MD, Residency Director, Department of Neurology, University of Chicago Medical Center, 5841 South Maryland, BH - Box 425, Chicago, IL 60637. (312) 702-0151.

NEUROLOGY RESIDENCY PGY-2 position Stanford University — An unexpected neurology residency position is available starting July, 1991 at Stanford University Medical Center. For further information, contact: Dr. Gregory W. Albers, Director, Residency Training Program, Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, CA 94305. Equal opportunity employer.

CHILD NEUROLOGY RESIDENCY: The Department of Neurology at the Medical College of Wisconsin has a first year position available for July 1, 1991 in a fully accredited three year training program at the new Children's Hospital of Wisconsin. There are five full-time pediatric neurologists conducting a strong general clinical neurology program with programs of special emphasis in both clinical and basic science in oncology, epilepsy, neurobehavior and neuromuscular disorders. Candidates should have two years of pediatric training in a ACGME accredited program. Contact: Richard J. Konkol, MD, PhD, Chief of the Section of Pediatric Neurology at 8701 Watertown Plank Road, Milwaukee, WI 53226. (414) 266-4090 or Eric Maas, MD, Neurology Residency Director at Froedtert Memorial Lutheran Hospital, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.

Faculty Positions

THE DEPARTMENT OF NEUROLOGY at the University of Louisville, School of Medicine is seeking a faculty member for a full-time academic appointment. Applicant must be board-eligible in neurology and neurodiagnostics, preferably with a completed fellowship in neurophysiology and electrodiagnostic medicine. Must be committed to education both at the undergraduate and graduate levels. Contact: William H. Olson, MD, Chairman, Department of Neurology, University of Louisville, Louisville, KY 40292. (502) 588-7981. EO/AAE.

THE UNIVERSITY OF MISSISIPPI Medical Center Department of Neurology invites applications for position of assistant professor from board-certified individuals with strong research, clinical and teaching skills. Persons with expertise in neuro-oncology, vascular disease and epilepsy are especially being sought. Please submit a letter of intent, curriculum vitae, and the names of three referring physicians to: Dr. James J. Corbett, Chairman, Department of Neurology, The University of Mississippi Medical Center, Jackson, MS 39216-4505. The University of Mississippi is an equal opportunity employer, M/F/H/V.

ACADEMIC NEUROLOGIST with board-eligibility in EMG sought by the Department of Neurology at The George Washington University Medical Center in Washington, DC. This non-tenure track, junior faculty position includes teaching responsibilities, patient care and the opportunity to develop a neuromuscular/EMG program. A competitive salary and excellent fringe benefits are provided. The George Washington University is an equal opportunity employer. Applications will be accepted until the position is filled. Please send inquiries and curriculum vitae to: Helene A. Emsellem, MD, Acting Chairman, Department of Neurology, 2150 Pennsylvania Avenue, NW, Suite 7-407, Washington, DC 20037.

ACADEMIC NEUROLOGIST with board-eligibility in clinical neurophysiology is sought by The Department of Neurology of The George Washington University Medical Center in Washington, DC. This tenure track position offers an opportunity to be involved in an active academic EEG/Sleep Laboratory and includes teaching and patient care activities. A competitive salary and excellent fringe benefits are provided. The George Washington University is an equal opportunity employer. Applications will be accepted until the position is filled. Please send inquiries and curriculum vitae to: Helene A. Emsellem, MD, Acting Chairman, Department of Neurology, 2150 Pennsylvania Avenue, NW, Suite 7-407, Washington, DC 20037.

LOYOLA UNIVERSITY Chicago Stritch School of Medicine, Department of Neurology invites applications for two positions at the assistant professor level. Applicants should be board-eligible or -certified in neurology and have subspecialty expertise in either epilepsy, movement disorders, cerebrovascular or neuromuscular diseases. Preference will be given to candidates with clinical research interests. Send CV to: Gastone Celesia, MD, Chairman, Neurology Department, Loyola University Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola University Chicago is an equal opportunity/affirmative action employer.

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NEUROLOGY PRACTICES for sale—Two established neurology practices for sale in Los Angeles County. A highly profitable, general neurology practice established over ten years, located on the campus of a major medical center in Burbank, California; and a busy pediatric neurology practice in Hollywood, California affiliated with major teaching and community hospitals. Call: Alex Guttman, Principal, Arthur S. Shorr and Associates, Inc., Consultants to Health Care Providers: (818) 348-6632.

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Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states
referred to as "delirium," "psychosis," or "encephalopathy," or rarely
dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels ar
reduction of phenytoin therapy is indicated if plasma levels are excessiv
termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advise
adhering strictly to the prescribed dosage regimen, and of informing the
condition in which it is not possible to take the drug orally as prescribe

Patients should also be cautioned on the use of other drugs or alcoholic
seeking the physician's advice.

Patients should be instructed to call their physician if skin rash devel

The importance of good dental hygiene should be stressed in
development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be neces
dosage adjustments.

Drug Interactions: There are many drugs which may increase or decre
which phenytoin may affect. Serum level determinations for phenytoi
when possible drug interactions are suspected. The most commonly occ
are listed below: 1. Drugs which may increase phenytoin serum levels
intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam,
estrogens, H_2-antagonists, halothane, isoniazid, methylphenid
phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide

2. Drugs which may decrease phenytoin levels include: carbamazepine
reserpine, and sucralfate. Moban® brand of molindone hydrochloride
which interfere with the absorption of phenytoin. Ingestion times of
preparations containing calcium should be staggered in patients with low
to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels
sodium valproate, and valproic acid. Similarly, the effect of phenytoin on
acid, and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants ma
susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is
include: corticosteroids, cou
digitoxin, doxycycline, estro
contraceptives, quinidine, r
vitamin D.

Drug/Laboratory Test Intera
cause decreased serum levels
(PBI). It may also produce lowe
dexamethasone or metyrapon
cause increased serum levels c
phatase, and gamma glutamy

Carcinogenesis: See "Warnin
tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women
phenytoin appears to be secreted in low concentrations in human mil

ADVERSE REACTIONS: Central Nervous System: The most common ma
with phenytoin therapy are referable to this system and are usually dos
nystagmus, ataxia, slurred speech, decreased coordination and ment
insomnia, transient nervousness, motor twitchings, and headaches have a
have also been rare reports of phenytoin induced dyskinesias, including
and asterixis, similar to those induced by phenothiazine and other neur

A predominantly sensory peripheral polyneuropathy has been obser
long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepa

Integumentary System: Dermatological manifestations sometimes ac
included scarlatiniform or morbilliform rashes. A morbilliform rash (n
common; other types of dermatitis are seen more rarely. Other more s
be fatal have included bullous, exfoliative or purpuric dermatitis, lupus e
Johnson syndrome, and toxic epidermal necrolysis (see Precautions)

Hemopoietic System: Hemopoietic complications, some fatal, have oc
in association with administration of phenytoin. These have included th
penia, granulocytopenia, agranulocytosis, and pancytopenia with or wi
pression. While macrocytosis and megaloblastic anemia have occurred,
respond to folic acid therapy. Lymphadenopathy including benign lymph
dolymphoma, lymphoma, and Hodgkin's Disease have been reported

Connective Tissue System: Coarsening of the facial features, enlarge
hyperplasia, hypertrichosis, and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is
such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadeno
lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal do
to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dy
tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. T
comatose and hypotensive. Death is due to respiratory and circulator

There are marked variations among individuals with respect to phen
toxicity may occur. Nystagmus, on lateral gaze, usually appears at
mcg/mL, dysarthria and lethargy appear when the plasma concentratio
as high a concentration as 50 mcg/mL has been reported without evid
as 25 times the therapeutic dose has been taken to result in a serum
mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote

The adequacy of the respiratory and circulatory systems should b
appropriate supportive measures employed. Hemodialysis can be co
is not completely bound to plasma proteins. Total exchange transfus
treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, incl
borne in mind.

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PI

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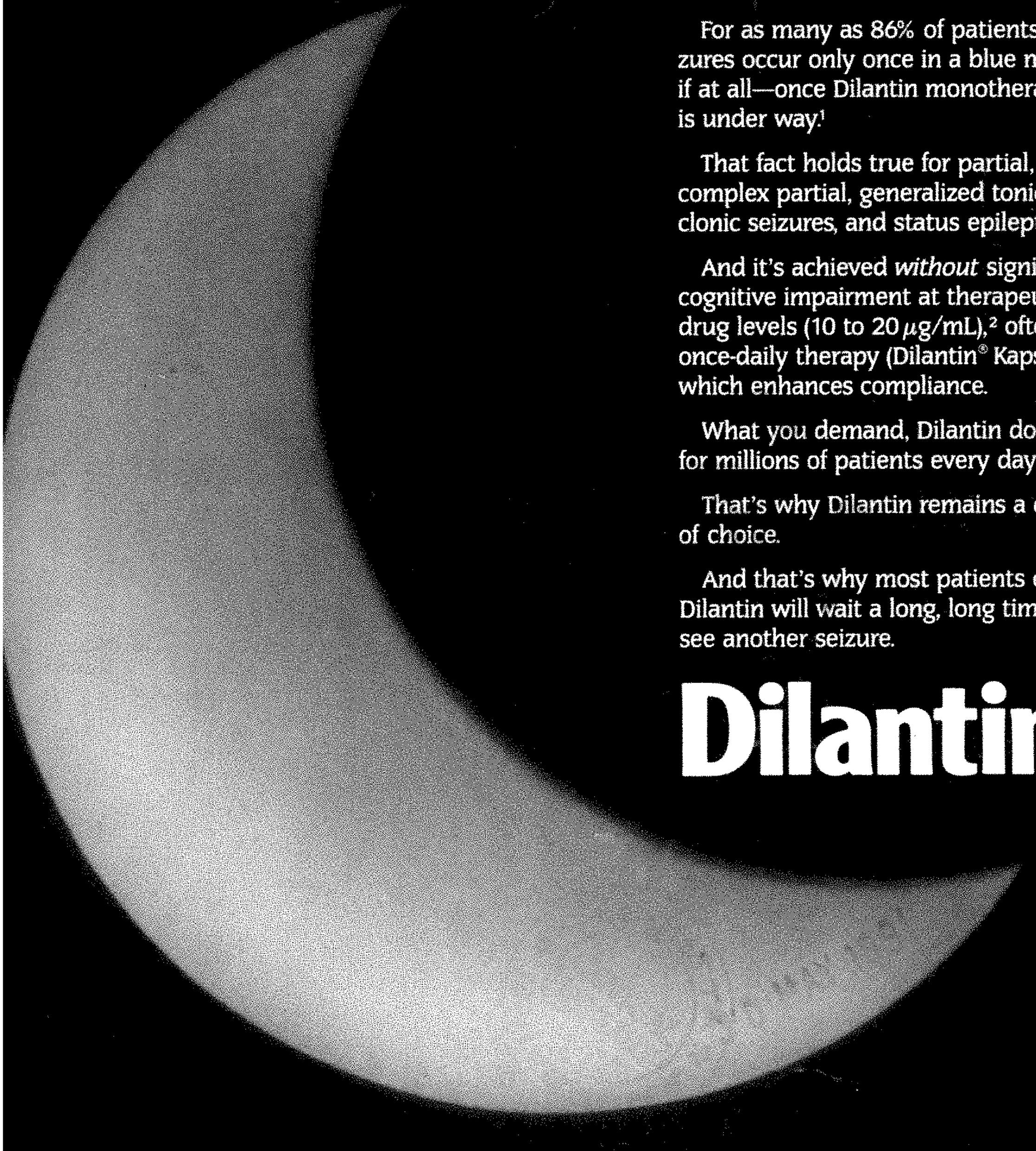

For as many as 86% of patients, seizures occur only once in a blue moon—if at all—once Dilantin monotherapy is under way.[1]

That fact holds true for partial, complex partial, generalized tonic-clonic seizures, and status epilepticus.

And it's achieved *without* significant cognitive impairment at therapeutic drug levels (10 to 20 μg/mL),[2] often *wit* once-daily therapy (Dilantin® Kapseals®), which enhances compliance.

What you demand, Dilantin does—for millions of patients every day.

That's why Dilantin remains a drug of choice.

And that's why most patients on Dilantin will wait a long, long time to see another seizure.

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Once in a blue moon" describes the phenomenon in which the moon appears as a brilliant blue. Seen worldwide following the volcanic eruption of Krakatoa in 1883, the blue moon occurs only when atmospheric cloud droplets, each less than 5 μm in diameter, form in abundance—an exceedingly rare event.[3]

References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976;31:292-296.

Please see adjacent page for brief summary of prescribing information.

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ARCHIVES
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Compensatory Mechanisms in Degenerative Neurologic Diseases: Insights From Parkinsonism
D. B. Calne, M. J. Zigmond

Corpus Callosotomy for Intractable Seizures in the Pediatric Age Group
R. E. Nordgren, A. G. Reeves, A. C. Viguera, D. W. Roberts

Intraputaminal Infusion of Nerve Growth Factor to Support Adrenal Medullary Autografts in Parkinson's Disease: One-Year Follow-up of First Clinical Trial
L. Olson, E.-O. Backlund, T. Ebendal, R. Freedman, B. Hamberger, P. Hansson, B. Hoffer, U. Lindblom, B. Meyerson, I. Strömberg, O. Sydow, Å. Seiger,

---

Prednisone in Duchenne Dystrophy: A Randomized, Controlled Trial Defining the Time Course and Dose Response
R. C. Griggs, R. T. Moxley III, J. R. Mendell, G. M. Fenichel, M. H. Brooke, A. Pestronk, J. P. Miller, and the Clinical Investigation of Duchenne Dystrophy Group

---

Positron Emission Tomography in Progressive Supranuclear Palsy
M. H. Bhatt, B. J. Snow, W. R. W. Martin, R. Peppard, D. B. Calne

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Volume 48, Number 4

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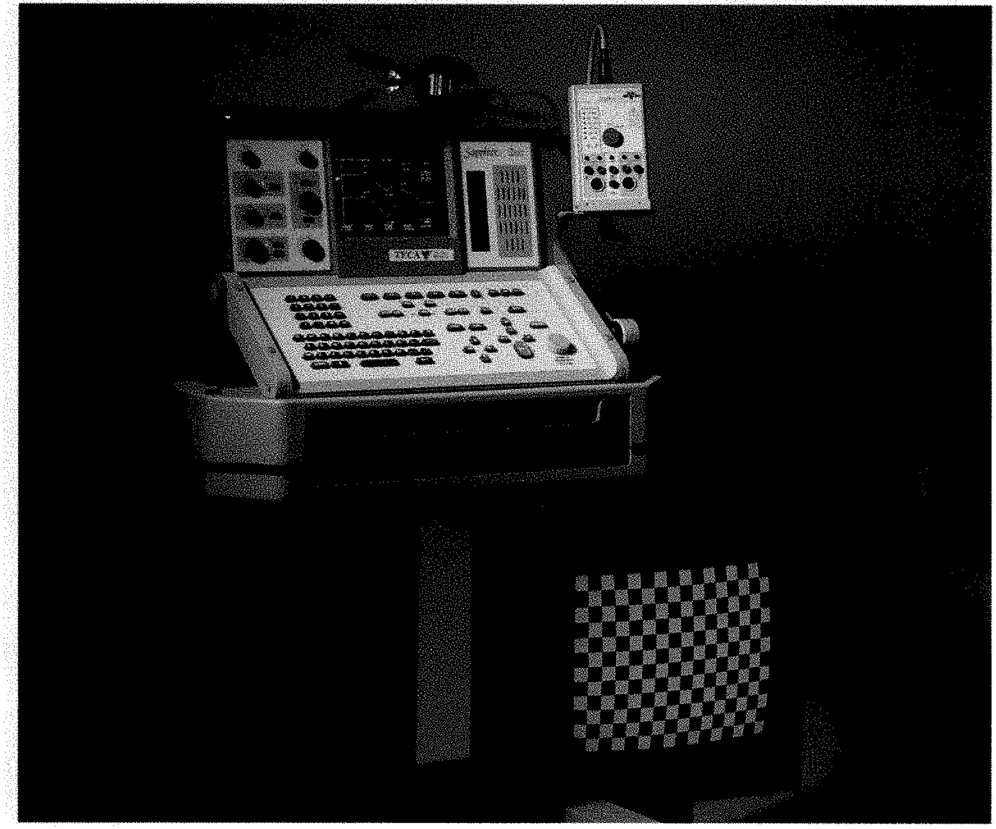

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INDERAL® LA (propranolol HCl) Long Acting Capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION:
CONSULT THE PACKAGE LITERATURE FOR FULL PRESCRIBING INFORMATION.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Use beta blockers with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia; other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, thus abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, tachycardia was replaced by severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Use with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity resulting in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, as both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of significant drug-induced toxicity in rats or mice, employing doses up to 150 mg/kg/day over an 18-month period. There were no drug-related tumorigenic effects at any dosage levels. No impairment of fertility attributable to the drug was seen in animal reproductive studies.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Exercise caution when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. The oculomucocutaneous reactions associated with practolol have not been reported with propranolol.

DOSAGE AND ADMINISTRATION: INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

For management of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis the dosage must be individualized. Usual initial dose is 80 mg once daily.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

PEDIATRIC DOSAGE – At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE. INDERAL is not significantly dialyzable. If ingestion is, or may have been, recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

BRADYCARDIA: Administer atropine (0.25 to 1.0 mg); if no response to vagal blockade, administer isoproterenol cautiously. CARDIAC FAILURE: digitalization and diuretics. HYPOTENSION: vasopressors, eg, levarterenol or epinephrine (there is evidence that epinephrine is the drug of choice). BRONCHOSPASM: administer isoproterenol and aminophylline.

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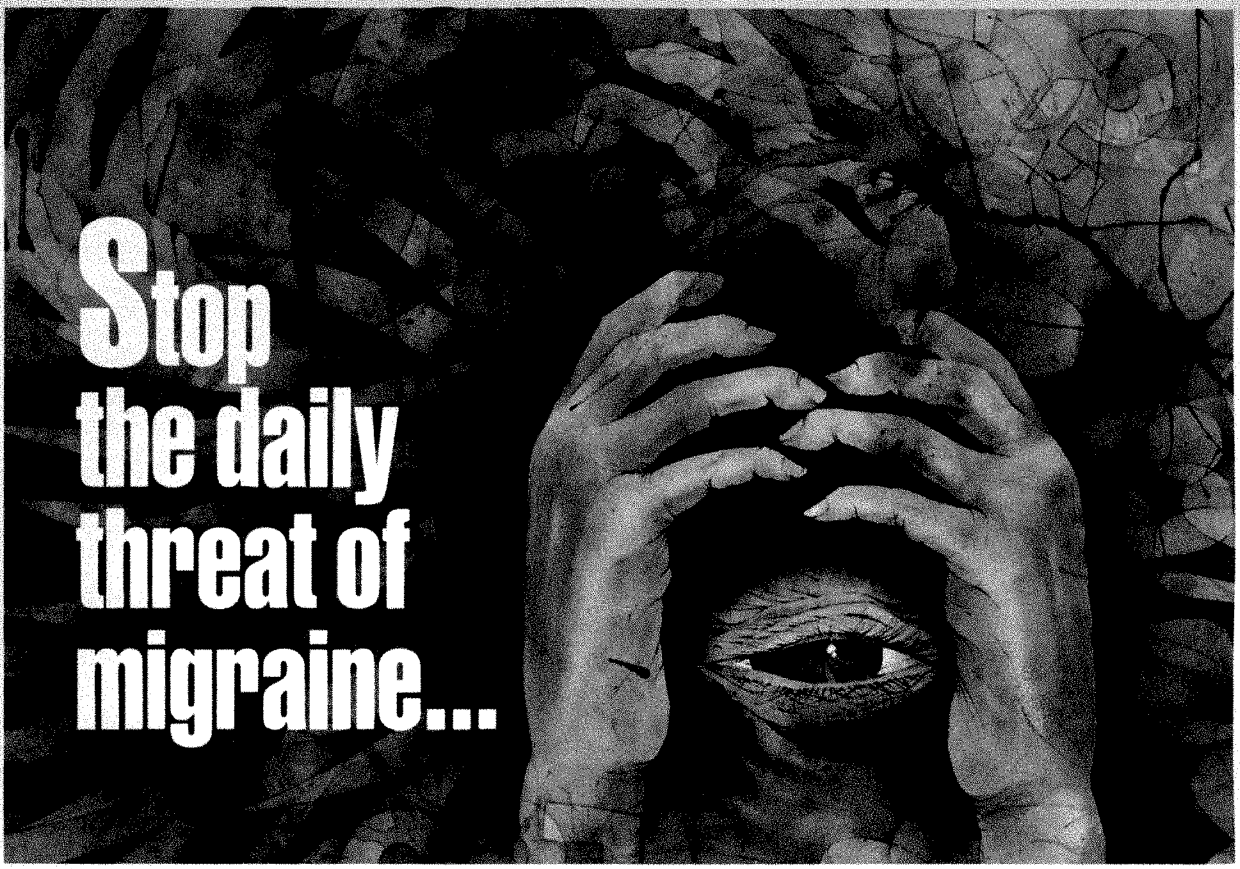
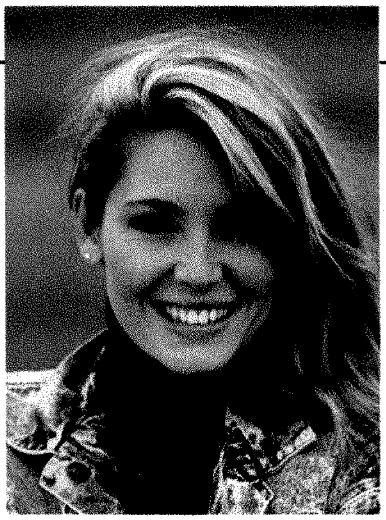


Stop the daily threat of migraine...

"Violent Passages" is a time-lapse portrayal by Louise Woodard depicting her own migraine headache sequence as she sees it. Her work focuses on the pain surrounding her eye and the confusion she feels as a result of the migraine.

with a daily dose of prevention.



Migraine. It's agonizing, debilitating, unpredictable. And abortive therapies often provide inadequate relief or cause troublesome side effects for your patients.

Proven qd prophylaxis at recommended doses.

Only INDERAL® LA provides once-daily preventive therapy— to significantly reduce both frequency and severity of common migraine. **Start with 80 mg/day and titrate to an effective dose — usually 160 to 240 mg once daily.**

Well-tolerated, long-term efficacy.

For patients whose day-to-day lives are undermined by anticipation of migraine, INDERAL LA can offer an improved sense of control. Because the only thing worse than the pain of migraine is the threat of it.

ONCE-DAILY
INDERAL® LA
(PROPRANOLOL HCl)
LONG ACTING CAPSULES
60, 80, 120, 160 mg

Another day without migraine.

Please see next page for brief summary of prescribing information.

INDERAL LA should not be used in the presence of congestive heart failure, sinus bradycardia, cardiogenic shock, heart block greater than first degree, and bronchial asthma.

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ARCHIVES OF Neurology

Vol 48 No. 4 APRIL 1991

LETTERS TO THE EDITOR

Brain-Stem Tuberculoma 358
Ricardo A. Rangel-Guerra, MD; Hector R. Martinez, MD;
Jose A. Garza, MD; Jesus Ancer, MD, Monterrey, Mexico

Brain-Stem Tuberculomas 359
Vedantam Rajshekhar, MCh, Hanover, NH

Cardiac Sources of Cerebral Embolism 359
Raul C. Rey; David A. Monteverde;
Roberto E. P. Sica, Buenos Aires, Argentina

Magnetic Resonance Evaluation of the Midbrain in Parkinson's Disease 360
P. Murali Doraiswamy, MD; Sunjay A. Shah;
Mustafa M. Husain, MD; P. Rodrigo Escalona, MD;
William M. McDonald, MD; Gary S. Figiel, MD;
K. Ranga R. Krishnan, MD, Durham, NC

In Reply
Steven J. Huber, PhD, Columbus, Ohio

SPECIAL ARTICLE

Compensatory Mechanisms in Degenerative Neurologic Diseases: Insights From Parkinsonism 361
Donald B. Calne, DM, Vancouver, British Columbia;
Michael J. Zigmond, PhD, Pittsburgh, Pa

ORIGINAL CONTRIBUTIONS

Corpus Callosotomy for Intractable Seizures in the Pediatric Age Group 364
Richard E. Nordgren, MD; Alexander G. Reeves, MD;
Adele C. Viguera; David W. Roberts, MD, Hanover, NH

Continued on page 348.

ARCHIVES

ntraputaminal Infusion of Nerve Growth Factor to Support \drenal Medullary Autografts in Parkinson's Disease:)ne-Year Follow-up of First Clinical Trial 373
.ars Olson, MD, Stockholm, Sweden;
rik-Olof Backlund, MD, Bergen, Norway;
'ed Ebendal, MD, Uppsala, Sweden;
:obert Freedman, MD, Denver, Colo; Bertil Hamberger, MD,
'er Hansson, MD, Stockholm, Sweden; Barry Hoffer, MD, Denver, Colo;
Jlf Lindblom, MD; Björn Meyerson, MD; Ingrid Strömberg, MD;
)lle Sydow, MD; Åke Seiger, MD, Stockholm, Sweden

'rednisone in Duchenne Dystrophy: \ Randomized, Controlled Trial Defining he Time Course and Dose Response 383
:obert C. Griggs, MD, Richard T. Moxley III, MD, Rochester, NY;
erry R. Mendell, MD, Columbus, Ohio;
;erald M. Fenichel, MD, Nashville, Tenn;
Aichael H. Brooke, MD, Edmonton, Alberta; Alan Pestronk, MD;
. Philip Miller, St Louis, Mo; and the Clinical Investigation
)f Duchenne Dystrophy Group

'ositron Emission Tomography in 'rogressive Supranuclear Palsy 389
Aohit H. Bhatt, MD; Barry J. Snow, MBChB, FRACP;
V. R. Wayne Martin, MD, FRCPC; Richard Peppard, MBBS, FRACP;
)onald B. Calne, DM, FRCP, FRCPC, Vancouver, British Columbia

diopathic Intracranial Hypertension Vithout Papilledema 392
ohn Marcelis, MD, Stephen D. Silberstein, MD, Philadelphia, Pa

Tuberous Sclerosis Complex in Olmsted County, Ainnesota, 1950-1989 400
Charles W. Shepherd, MB, MRCP; C. Mary Beard RN, MPH;
Aanuel R. Gomez, MD; Leonard T. Kurland, MD, DPH;
ack P. Whisnant, MD, Rochester, Minn

Standard and Controlled-Released Levodopa/ Carbidopa in Patients With Fluctuating Parkinson's Disease on a Protein Redistribution Diet: A Preliminary Report 402
Patricia J. Karstaedt, MD; Jonathan H. Pincus, MD;
Steven S. Coughlin, PhD, Washington, DC

***Pneumocystis carinii* Pneumonia in Patients With Primary Brain Tumors** 406
John W. Henson, MD; Jai K. Jalaj, MD;
Russell W. Walker, MD; Diane E. Stover, MD;
Anna O. S. Fels, MD, New York, NY

Neuroanatomic Differences Between Dyslexic and Normal Readers on Magnetic Resonance Imaging Scans 410
Ranjan Duara, MD, Miami Beach, Fla; Alex Kushch; Karen Gross-Glenn, PhD;
W. William Barker, MS; Bonnie Jallad, MS; Shlomo Pascal, MD;
David A. Loewenstein, PhD; Jerome Sheldon, MD, Miami Beach, Fla;
Mark Rabin, PhD; Bonnie Levin, PhD; Herbert Lubs, MD, Miami, Fla

Continued on page 351.

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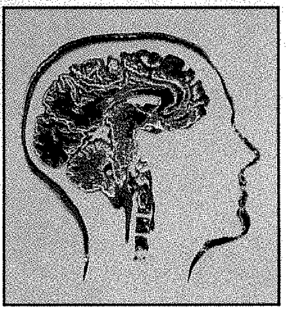


CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

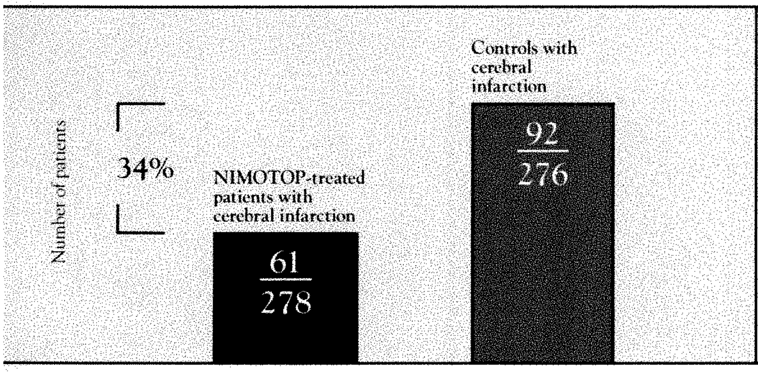
REDUCES INCIDENCE OF CEREBRAL NFARCTION IN PATIENTS FOLLOWING SUBARACHNOID HEMORRHAGE

---

n the largest study to date, NIMOTOP demonstrated a significant eduction in incidence of cerebral infarction[1]

- Twenty-two percent (61/278) of NIMOTOP-treated patients experienced cerebral infarction vs. 33% (92/276) of controls
- NIMOTOP reduced the incidence of cerebral infarction by 34%

hirty-four percent reduction in incidence of cerebral infarction with IMOTOP-treated patients vs. controls (n=554; p=0.003)[1]*



*90% of patients in this study were Hunt and Hess Grades I-III.

Dose: 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 days commencing within 96 hours of SAH.

Adapted from Pickard, et al.[1]

IMOTOP modulates calcium influx to promote cerebral perfusion, nd may directly protect neurons[2-5]

[In animals] The beneficial cytoprotective effect of nimodipine, probably related to normalization f calcium homeostasis and blood-brain barrier permeability after ischemia, may reflect both ascular and cellular sites of action."[6]

azarewicz JW, et al. *Stroke* 1989.

[In humans] The data thus suggest that nimodipine neither prevents nor reverses cerebral asospasm. Calcium channel blockers such as nimodipine may have an effect on cerebral arterioles hat are below the limits of resolution of angiography...."[1]

ickard JD, et al. *Br Med J* 1989.

MILES

lease see references and Brief Summary of full prescribing information on next page

CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

NIMOTOP REDUCES THE INCIDENCE OF CEREBRAL NFARCTION FOLLOWING SUBARACHNOID HEMORRHAGI

EF SUMMARY
OTOP® (nimodipine/Miles) CAPSULES
Oral Use

ICATIONS AND USAGE

imotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm wing subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral otop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue 1 days.

NTRAINDICATIONS

one known.

CAUTIONS

eneral: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium nnel blocker, although they are generally not marked. In patients with subarachnoid hemor- e given Nimotop® in clinical studies, about 5% were reported to have had lowering of the d pressure and about 1% left the study because of this (not all could be attributed to odipine). Nevertheless, blood pressure should be carefully monitored during treatment with otop® based on its known pharmacology and the known effects of calcium channel blockers. epatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic tion. Such patients should have their blood pressure and pulse rate monitored closely and ld be given a lower dose (see Dosage and Administration).

aboratory Test Interactions: None known.

rug Interaction: It is possible that the cardiovascular action of other calcium channel kers could be enhanced by the addition of Nimotop®.

Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive pounds taken concomitantly by patients suffering from hypertension: this phenomenon was observed in North American clinical trials.

arcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences denocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats n a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) in placebo controls. The differences were not statistically significant; however, the higher s were well within historical control range for these tumors in the Wistar strain. Nimodipine found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm odipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. agenic studies, including the Ames, micronucleus and dominant lethal tests were negative. imodipine did not impair the fertility and general reproductive performance of male and ale Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of nancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg ent.

regnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect imalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by ge) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not 0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence unted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryo- c, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day inistered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of ng/kg/day nimodipine administered by gavage from day 16 of gestation and continued until ifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of etal variation, stunted fetuses and stillbirths but no malformations. There are no adequate well controlled studies in pregnant women to directly assess the effect on human fetuses. odipine should be used during pregnancy only if the potential benefit justifies the potential to the fetus.

ursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk oncentrations much higher than in maternal plasma. It is not known whether the drug is reted in human milk. Because many drugs are excreted in human milk, nursing mothers are ised not to breast feed their babies when taking the drug.

ediatric Use: Safety and effectiveness in children have not been established.

VERSE REACTIONS

dverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage 2%) who were given nimodipine. The most frequently reported adverse experience was reased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated ents also reported adverse experiences. The events reported with a frequency greater than 1% displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
n/Symptom	0.35 mg/kg (n = 82)	30 mg (n = 71)	60 mg (n = 494)	90 mg (n = 172)	120 mg (n = 4)	(n = 479)
reased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
ormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
ma	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
rrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
h	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
dache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
strointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0

DOSE q4h
Number of Patients (%)

	Nimodipine					Placel
Sign/Symptom	0.35 mg/kg (n = 82)	30 mg (n = 71)	60 mg (n = 494)	90 mg (n = 172)	120 mg (n = 4)	(n = 4
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytoper anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lighth dedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group we itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiti diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; dissemina intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based increased incidence with higher dose or a higher rate compared to placebo control, inclu decreased blood pressure, edema and headaches which are known pharmacologic action calcium channel blockers. It must be noted, however, that SAH is frequently accompanied alterations in consciousness which lead to an under reporting of adverse experiences. Patie who received nimodipine in clinical trials for other indications reported flushing (2.1 headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. calcium channel blocker, nimodipine may have the potential to exacerbate heart failure susceptible patients or to interfere with A-V conduction, but these events were not observed

No clinically significant effects on hematologic factors, renal or hepatic function or carbo drate metabolism have been causally associated with oral nimodipine. Isolated cases of non- ing elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet cou (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have b reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Sy toms of overdosage would be expected to be related to cardiovascular effects such as exces peripheral vasodilation with marked systemic hypotension. Clinically significant hypotens due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bou dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subara noid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconsci a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of capsule extracted into a syringe. The contents should then be emptied into the patient's in naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately dou C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pres and heart rate.

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REFERENCES

1. Pickard JD, Murray GD, Illingworth R, et al. *Br Med J.* 1989;298:636-642. 2. Solomon Fink ME. *Arch Neurol.* 1987;44:769-773. 3. Petruk KC, West M, Mohr G, et al. *J Neuros* 1988;68:505-517. 4. Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. *Acta Ne Scand.* 1987;76:267-271. 5. Scriabine A, van den Kerckhoff W. *Ann NY Acad Sci.* 1988;522: 706. 6. Lazarewicz JW, Pluta R, Salinska E, Puka M. *Stroke.* 1989;20:70-77.

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ARCHIVES

Magnetic Resonance Imaging White Matter Lesions and Cognitive Impairment in Hypertensive Individuals 417
Reinhold Schmidt, MD; Franz Fazekas, MD; Hans Offenbacher, MD; Helene Lytwyn, PhD; Brigitte Blematl, MD; Kurt Niederkorn, MD; Susanna Horner, MD; Franz Payer, MD; Wolfgang Freidl, PhD, Graz, Austria

HISTORY OF NEUROLOGY

Visual Art in the Neurologic Career of Jean-Martin Charcot 421
Christopher G. Goetz, MD, Chicago, Ill

OBSERVATIONS

Internal Capsule Plaque and Tonic Spasms in Multiple Sclerosis 427
Davide Maimone, MD, Anthony T. Reder, MD, Chicago, Ill; Francesco Finocchiaro, MD, Egidio Recupero, MD, Catania, Italy

Hypothalamic or Central Obesity Is Associated With an Early Rise in Plasma Insulin Concentration 429
Michael M. Segal, MD, PhD; Jennifer Bell, MD; Gary M. Abrams, MD, New York, NY

Right Parietal Stroke With Gerstmann's Syndrome: Appearance on Computed Tomography, Magnetic Resonance Imaging, and Single–Photon Emission Computed Tomography 432
Matthew R. Moore, MD; Jeffrey L. Saver, MD; Keith A. Johnson, MD; Jorge A. Romero, MD, Boston, Mass

Neurologic Complications of the Tryptophan–Associated Eosinophilia–Myalgia Syndrome 436
Lynn M. Tolander, MD; Colin R. Bramford, MD; Mark T. Yoshino, MD; Samuel Downing, MD; George Bryan, MD, Tucson, Ariz

Magnetic Resonance Imaging of Fourth Ventricular Epidermoid Tumors 438
William A. Wagle, MD; Bruce Jaufmann, MD; J. Ernest Mincy, MD, Albany, NY

REGULAR DEPARTMENTS

Calendar 353

Instructions for Authors 357

Index to Advertisers 352

Classified Advertising 441

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INDEX TO ADVERTISERS

Berlex Imaging 360A-D

Webb Dordick 448
Downstate Headache Center 352

Geigy Pharmaceuticals 352A-B, 416A-B

Eli Lilly & Company 388A-D

Medical College of Virginia 352
Miles Pharmaceuticals 349-350

Parke-Davis .... Cover 3-Cover 4

Sandoz Pharmaceuticals 354-356, 446-448

TECA Corporation 382

Wyeth-Ayerst Laboratories .... Cover 2-346

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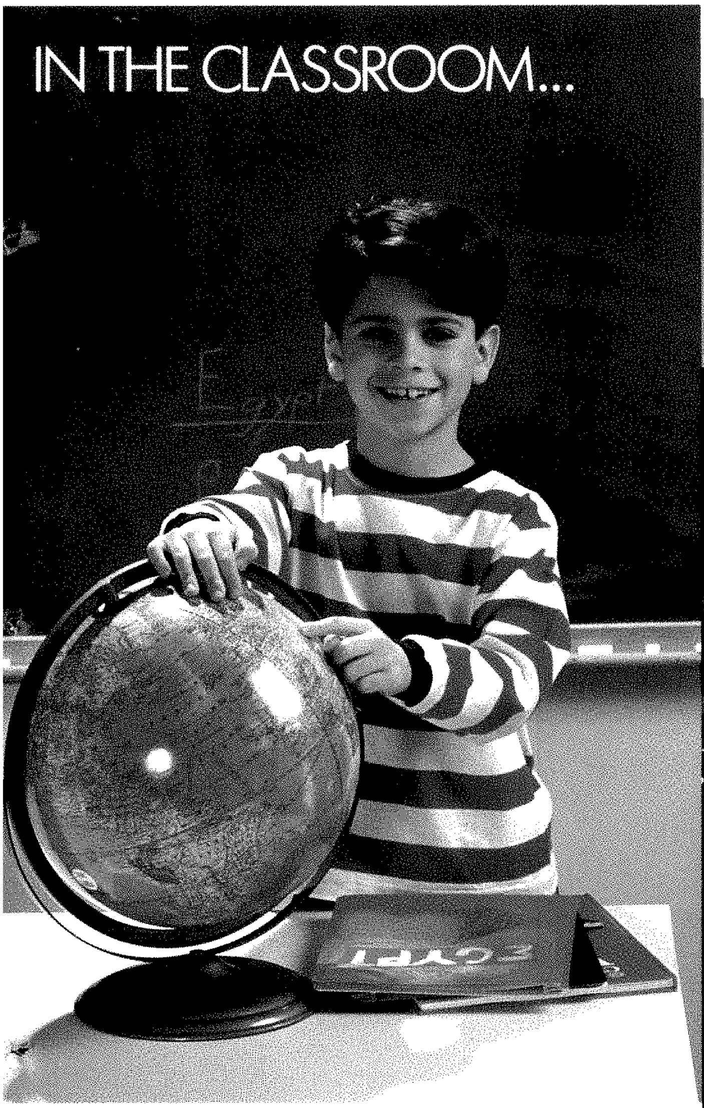
Seizures controlled, thoughts clear, smiles bright



Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

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Tegretol®

200 mg scored tablets
100 mg chewable tablets

carbamazepine USP

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References
1. Smith DB, Mattson RH, Cramer JA, et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58.
2. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151.
3. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;29:794-804.

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink Tablets of 200 mg—pink

WARNING
APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

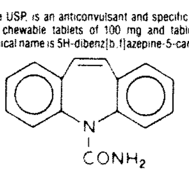
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is:



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of ^{14}C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

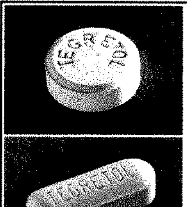
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System. Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin. Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary.

Cardiovascular System. Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver. Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System. Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System. Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System. Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System. Aching joints and muscles, and leg cramps.

Metabolism. Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration. Irregular breathing, respiratory depression.

Cardiovascular System. Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles. Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract. Nausea, vomiting.

Kidneys and Bladder. Anuria or oliguria, urinary retention.

Laboratory Findings. Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning. When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug. Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption. Activated charcoal, laxatives.

Measures to Accelerate Elimination. Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression. Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock. Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions. Diazepam or barbiturates.

Warning. Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities. If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) ^{59}Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture.

Dispense in tight container (USP).

Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles.

Printed in U.S.A. C90-34 (Rev. 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

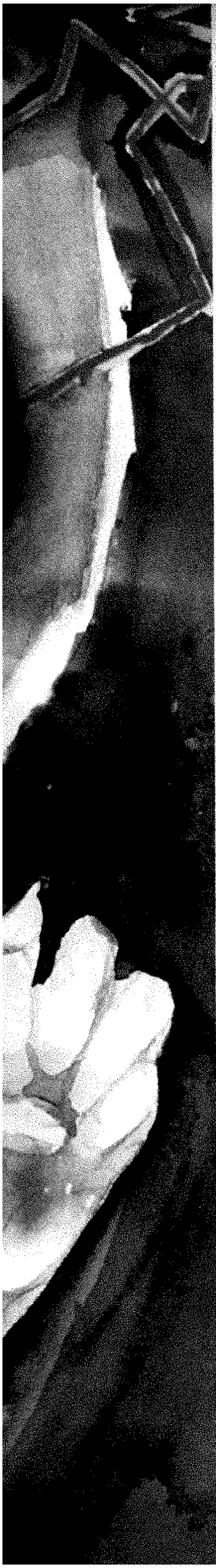
Calendar

CALENDAR OF MEETINGS

1991		
March	7-9	"Recent Advances in Geriatric Medicine, New Treatment Options for Old Problems," The Pan Pacific Hotel, San Diego, Calif. Contact Cass Jones, Professional Conference Management Inc, 7916 Convoy Ct, San Diego, CA 92111; (619) 565-9921.
	14-16	"Brain Chemistry and Behavior: Advances in Positron Emission Tomography and Single Photon Emission Tomography Imaging," Baltimore, Md. Contact Patty Campbell, Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-3839.
	16-20	Fifth Annual Magnetic Resonance Imaging Conference, Marriott's Camelback Inn, Scottsdale, Ariz. Contact Kevin King, Education Coordinator, Radiologic Education Center, St Joseph's Hospital and Medical Center, 350 W Thomas Rd, Phoenix, AZ 85013; (602) 285-3956.
	17-21	The Eighth Conference of the Southeast European Society for Neurology and Psychiatry, Jerusalem, Israel. Contact Shaul Feldman, MD, PO Box 50006, Tel Aviv 61500, Israel.
	17-23	24th Latin American Congress of Neurosurgery, Miami, Fla. Contact Sergio Gonzalez-Arias, MD, 8950 N Kendall Dr, Suite 406, Miami, FL 33176; (305) 271-6159.
	18-20	"Spectrum of Developmental Disabilities: Cerebral Palsy: Issues of Early Detection and Intervention," The Johns Hopkins Medical Institutions, Baltimore, Md. Contact Program Coordinator, The Johns Hopkins Medical Institutions, Office of Continuing Education, Turner Bldg, 720 Rutland Ave, Baltimore, MD 21205; (301) 955-2959.
	21-33	"Recent Advances in Neurology and Neurosurgery," Scottsdale, Ariz. Contact Toby A. Jardine, Manager, Administration, Barrow Neurological Institute, 350 W Thomas Rd, Phoenix, AZ 85013; (602) 285-3178.
	23-24	Cervical and Lumbar Spine: State of the Art '91, Hyatt Regency Embarcadero, San Francisco, Calif. Contact the San Francisco Spine Institute, 1850 Sullivan Ave, Suite 140, Daly City, CA 94015; (415) 991-6761.
April	6	"Child Neuropsychology: Cognitive Development and Disorder." New York (NY) University Medical Center. Contact Karen Webb, PhD, New York Neuropsychology Group, Mount Sinai Medical Center, 19 E 98th St, Box 1228, New York, NY 10029; (212) 241-6148.
	10-11	The Second Annual Postgraduate Electromyography Review Course, Iowa City, Iowa. Contact Deborah L. Hatz, Program Coordinator, University of Iowa College of Medicine, Iowa City, IA 52242; (319) 335-8598.
	21-27	43rd Annual Meeting of the American Academy of Neurology, Hynes Convention Center, Boston, Mass. Contact American Academy of Neurology, 2221 University Ave SE, Suite 335, Minneapolis, MN 55414; (612) 623-8115.
	22	The Annual Meeting of the World Federation of Neurology Research Group on Neuroepidemiology, Boston, Mass. Contact Gustavo C. Román, Chief, Neuroepidemiology Branch, Federal Building, Room 714, 7550 Wisconsin Ave, National Institutes of Health, Bethesda, MD 20892; (301) 496-1714.
	27-28	1991 Neuroradiology Review Course, Oak Brook (Ill) Hills Hotel and Conference Center. Contact Continuing Medical Education, Loyola University Stritch School of Medicine, 2160 S First Ave, Maywood, IL 60153; (708) 216-3236.
	29-May 5	Advances in Internal Medicine, The Towsley Center, Ann Arbor, Mich. Contact Julie Jacobs, Office of Continuing Medical Education, G-1100 Towsley Center, Box 0201, University of Michigan Medical School, Ann Arbor, MI 48109-0201; (313) 763-1400.
May	6-8	"Neurotoxins and Their Potential Role in Neurodegeneration," Adams Mark Hotel, Philadelphia, Pa. Contact Marketing Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212) 838-0230.
	7-10	Ecuadoran Society of Neurology, Quito, Ecuador. Contact Ecuadoran Society of Neurology, PO Box 2821, Quito, Ecuador.
	16-18	"Neurosurgical/Neurological Intensive Care: Update and Review," The Cleveland (Ohio) Clinic Foundation. Contact The Cleveland Clinic Foundation, Department of Continuing Education, 9500 Euclid Ave, Room TT-31, Cleveland, OH 44195-5241; 1-800-762-8173.
	17-18	"Pediatric Neurology for the '90's," Wilmington, Del. Contact Jeanne Cole, Continuing Medical Education Office, Alfred I. duPont Institute, 1600 Rockland Rd, Wilmington, DE 19899; (302) 651-6753.
	27-29	New Frontiers on Acute Ischemic Stroke-An Update, Rome, Italy. Contact Stroke Secretariat, Via Bertolini, 26/B, 00197 Rome, Italy.
	30-June 1	International Conference on Stroke, Geneva, Switzerland. Contact N. M. Bornstein, MD, International Conference on Stroke, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211 Geneva, Switzerland.
June	1-6	The 15th International Symposium on Cerebral Blood Flow and Metabolism, James L. Knight International Center, Miami, Fla. Contact Ms Jenny Bernal, Conference Coordinator, Brain '91, University of Miami Conference Center, 400 SE Second Ave, Fourth Floor, Miami, FL 33131.
	2-6	Ninth International Congress of Electromyography, Jerusalem, Israel. Contact Dr Arieh N. Gilai, Convener, EMG-CN-IX Congress, PO Box 29334, Tel Aviv 61292, Israel.
	10-13	Twelfth Annual Child Neurology Postgraduate Course, Sonesta Beach Hotel, Key Biscayne, Fla. Contact Oscar Papazian, MD, Department of Neurology, Miami Children's Hospital, 3200 SW 60th Ct, Miami, FL 33155; (305) 662-8330.
	19-22	The 26th Annual Meeting of the Canadian Congress of Neurological Sciences, Halifax (Nova Scotia) Sheraton. Contact Permanent Secretariat, Canadian Congress of Neurological Sciences, 810-906 12th Ave SW, Calgary, Alberta, Canada T2R 1K7; (403) 229-9544.
	21-23	"Current Concepts in Child Neurology," Hyatt Islandia Hotel, San Diego, Calif. Contact Continuing Medical Education, Children's Hospital and Health Center, 8001 Frost St, San Diego, CA 92123; (619) 576-1700.

HEADACHE DESCRIBED

"Headache"—a personal interpretation of headache pain by John Crowley, a headache patient.



HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL WITH CODEINE (III) CAPSULES

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

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FWC-0790-01

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming], butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Placebo (N = 377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

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[NOVEMBER 1, 1990 FWC-Z26]

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Brain-Stem Tuberculoma

To the Editor.—It is with interest that we read the article entitled "Brain-Stem Tuberculoma, An Analysis of 11 Patients" written by Talamás et al[1] that appeared in the May 1989 issue of the ARCHIVES.

It is a well-known fact that the diagnosis of central nervous system tuberculosis is a very difficult one, especially because of the wide variety of clinical presentation of this disease. Recently, the development of neuroimaging methods and several immunological techniques, including the enzyme-linked immunosorbent assay method, for tuberculous antigens, has increased the accuracy of this diagnosis. However, there are still some cases in which the definitive diagnosis has to be made through brain or meningeal biopsy specimens.

Of the 11 cases presented in this article, only in one patient was the diagnosis proved through histological findings, and in the remaining 10 patients, "it was supported or inferred through clinical presentation, cerebrospinal fluid analysis, computed tomography, or magnetic resonance imaging, and response to antituberculous therapy." The clinical manifestations of central nervous system tuberculosis are variable and unspecific, and they are very difficult to differentiate from tumors, fungal and parasitic disease, or vasculitides of the brain stem. The cerebrospinal fluid analysis in these cases did not show specific changes (hyperproteinorrachia in four cases and mild pleocytosis in three patients). The glucose levels and immunological test results were not reported. At the present time, there are new techniques for the detection of *Mycobacterium tuberculosis*-specific markers in the cerebrospinal fluid, such as frequency-pulsed electron-capture gas-liquid chromatography (specificity, 90%); enzyme-linked immunosorbent assay (specificity, 95%); latex particle agglutination (specificity, 99%); and serum enzyme-linked immunosorbent assay (specificity, 94% to 100%),[2] which could have been performed, at least in the latter cases reported by the authors. We agree with the author's discussion about the value of computed tomographic findings in the diagnosis of central nervous system tuberculosis, but Fig 4, which apparently shows improvement of the brain-stem lesion due to antituberculous therapy, cannot be postulated as such because the follow-up computed tomographic scan shows a different axial level. In regard to magnetic resonance imaging findings, the T_2-weighted image in Fig 1 shows a high-intensity signal lesion involving most of the brain stem and part of the cerebellum, which, according to our experience, may represent meningoencephalovasculitis,[3] infiltrating glioma, metastatic tumor, or fungal infection. We have a similar case (Fig 1) which corresponded on postmortem examination to a tuberculosis meningoencephalovasculitis, which simulated, even at gross examination, an infiltrating brain-stem glioma (Fig 2).

The authors based the diagnosis of brain-stem tuberculoma in most cases on the fact of the response to antituberculous therapy, but this assumption cannot be supported in cases Nos. 6 and 10.

We want to emphasize that brain-stem tuberculoma has to be differentiated from other pathologic findings of this neuroanatomical region, including the form of central nervous system tuberculosis called *tuberculous meningoencephalovasculitis*, which can simulate brain-stem infiltrating glioma, such as was demonstrated in our case that was presented elsewhere[3] (Figs 1 and 2).

In summary, we conclude that the diagnosis of brain-stem tuberculoma should not be supported mainly through the response to antituberculous therapy, but only with the rational use of other diagnostic methods

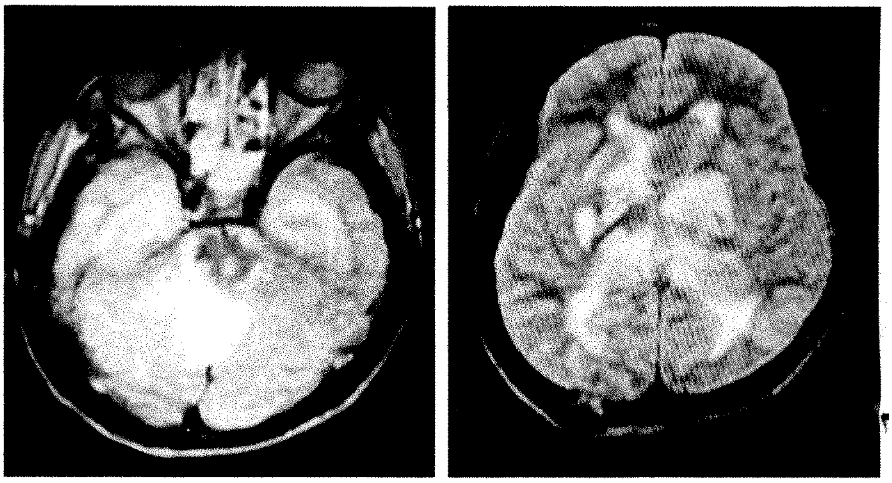
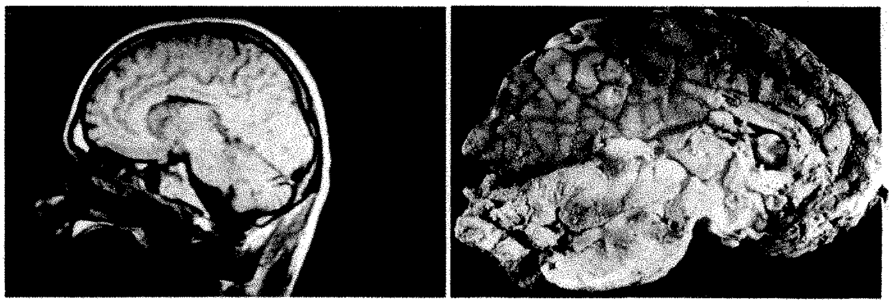


Fig 1.—Left, High-intensity signal in the brain stem and part of the cerebellum; an irregular hypointense area is observed in the center of the brain stem (80/2000). Right, Multiple high-intensity signal areas in the periventricular region and basal ganglia (80/2000).

Fig 2.—Left, Isointense lesion involving the brain-stem simulating an infiltrating glioma (28/500). Right, Sagittal cut of the brain showing an infiltrating lesion in the brain stem.



such as immunological tests in cerebrospinal fluid (with well-known specificity), as well as computed tomography and magnetic resonance imaging,[4,5] and, in selected cases, through neuropathological examination.

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1. Talamás O, Del Brutto OH, Garcia-Ramos G. Brain-stem tuberculoma: an analysis of 11 patients. *Arch Neurol.* 1989;46:529-535.
2. Gandy SE. Tuberculosis of the central nervous system: recent experience and reappraisal. In: Plum F, ed. *Advances in Contemporary Neurology.* Philadelphia, Pa: FA Davis Co, 1988:153-183.
3. Martinez HR, Rangel RA, Garza JE, Ancer J. Central nervous system tuberculosis (CNS-TB) simulating brain stem glioma on MRI. Presented at the 12th Annual Meeting of the American Society of Neuroimaging, Orlando, Fla: February 22-26, 1989:10.
4. Prince HI, Danziger A. Computed tomography in cranial tuberculosis. *Am J Roentgenol.* 1978;130:769-771.
5. Schroth G, Kretzchmar K, Gawehn J, Voigt K. Advantage of magnetic resonance imaging in the diagnosis of cerebral infections. *Neuroradiology.* 1987;29:120-126.

Brain-Stem Tuberculomas

To the Editor.—It was with great interest that I read the article on brain-stem tuberculomas by Talamas et al.[1] I am concerned about the diagnosis in patients 3 and 8. In both these patients, there were single, isolated brain-stem masses and neither had evidence of systemic tuberculosis. Diagnosis in these patients was based either on the disappearance of the lesion in the computed tomographic scan (patient 3) or clinical improvement (patient 8), following antituberculous therapy. Our experience shows that these criteria are not foolproof. For a number of years single, small, enhancing lesions noted on computed tomography in Indian patients with seizures were diagnosed as tuberculomas and treated accordingly on the basis of the above criteria (ie, disappearance on the scan or clinical improvement with antituberculous therapy).[2] After excision biopsy specimens (using computed tomographic-guided stereotaxic localization) were obtained in 15 consecutive patients, we proved that, in nearly all cases, these lesions were caused by cysticercosis and needed no specific therapy.[3] Thus it is important to consider other inflammatory or demyelinating disorders in such cases, and one cannot be categorical in making a diagnosis of a tuberculous lesion. Second, it is rare for tuberculomas to occur as isolated single brain-stem masses (ie, without any other coexistent brain masses) in the absence of active systemic tuberculosis or tuberculous meningitis. In our center, patients with tuberculomas are still seen quite often. However, in a consecutive series of eight patients with isolated brain-stem masses, who underwent computed tomographic-guided stereotaxic biopsy, there were no tuberculomas. This underlines the fact that, even in endemic areas such as ours, a tuberculoma only rarely presents as an isolated brain-stem mass. Third, exposure to tuberculosis alone (patient 3) cannot be considered as adequate evidence to support the diagnosis of a tuberculoma, because there is a high incidence of such an exposure in the general patient population in developing countries.

A confident diagnosis of a brain-stem tuberculoma without histologic proof can only be considered in patients with active systemic tuberculosis or tuberculous meningitis, and more so if there are multiple lesions involving other areas of the brain. In all other cases a histologic diagnosis should be obtained, as empirical antituberculous therapy may delay appropriate therapy. In the case of isolated brain-stem masses computed tomographic-guided stereotaxic biopsy would be the ideal procedure.

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1. Talamas O, Del Brutto OH, Garcia-Ramos G. Brain-stem tuberculoma: an analysis of 11 cases. *Arch Neurol.* 1989;46:529-535.
2. Bhargava S, Tandon PN. Intracranial tuberculomas: a CT study. *Br J Radiol.* 1980;53:935-941.
3. Chandy MJ, Rajshekhar V, Prakash S, et al. Cysticercosis causing single small CT lesions in Indian patients with seizures. *Lancet.* 1989;1:390-391.

Cardiac Sources of Cerebral Embolism

To the Editor.—We read with interest the second report on brain embolism by the Task Force.[1] In reviewing their first article,[2] they estimated that the incidence of stroke due to cardiogenic embolism should be around 15%, ranging between 6% and 23%, of all ischemic strokes. When discussing heart pathologies, they established that nonvalvular atrial fibrillation, ischemic heart disease, rheumatic heart disease, and prosthetic cardiac valves account for the majority of cardioembolic stroke and considered that nonischemic dilated cardiomyopathies were a less common cardiac cause of embolism. These data have been obtained from studies published in the English-language literature and encompass reports originated mainly in the Northern Hemisphere. However, it is reasonable to assume that other areas in the world may have a different incidence of heart disease, causing embolic brain damage, due to the presence of regional predisposing factors.

Recently, we reviewed our own data consisting of 367 patients who were assessed at our stroke clinic between 1983 and 1989. All of these patients had a diagnosis of ischemic stroke based on clinical findings and brain computed tomographic scan. The criteria employed for the diagnosis of cardioembolic stroke included the following: (1) sudden onset and maximal neurological focal deficit from the very beginning of the episode, (2) brain computed tomographic scan showing an ischemic lesion, or features consistent with cardioembolic stroke (ie, hemorrhagic infarct or multiple cortical infarcts in different vascular territories (images consistent with lacunar strokes were excluded), (3) M-mode and bidimensional echocardiography, or cardiac catheterization showing the heart as the source of the emboli, and (4) absence of stenotic-occlusive cerebrovascular disease by cerebral angiography, when performed in the group of patients with probable atherosclerotic vascular disease.

Forty-seven patients (12.8%) filled the criteria for being considered affected by brain embolism of cardiac origin. The group was composed of 21 women and 26 men. Their ages ranged between 26 and 79 years (mean, 54 years). The emboligenic heart disorders found included the following: (1) nonvalvular atrial fibrillation in 13 patients (27.6%), (2) rheumatic heart disease in 10 patients (21.2%), (3) nonischemic dilated cardiomyopathy in eight patients (17%), and (4) ischemic heart disease in seven patients (14.9%). The remaining nine patients (19.7%) had other conditions; namely, bacterial endocarditis (three patients), mitral valve prolapse (two patients), nondilated cardiomyopathy (two patients), prosthetic cardiac valve (one patient), and congenital heart malformation (one patient). From the eight patients who had nonischemic dilated cardiomyopathy, five (62%) had cardiac involvement due to Chagas' disease.

Taken together, our figures show that, although they are well in line with the current literature,[1] nonischemic dilated cardiomyopathy is one of the main causes of ischemic stroke due to cardiac embolism in our community. Most likely, this reflects the presence of regional factors, Chagas' disease in the present series, which may not play any role in other geographic areas. Chagas' disease is an endemic parasitic illness in our country (and in all Latin America[3]), leading to involvement of the heart yielding a nonischemic dilated cardiomyopathy that, in turn, may be the cause of ischemic embolic stroke.[4]

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2. Cerebral Embolism Task Force. Cardiogenic brain embolism. *Arch Neurol.* 1986;43:71-84.
3. Organisation Mondiale de la Santé. Les maladies transmissibles dans les Ameriques. *Chron Org Mond Santé.* 1975;29:155.
4. Oliveira JSM, Correa de Araujo RR, Navarro MA, Muccillo G. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. *Am J Cardiol.* 1983;52:147-151.

Magnetic Resonance Evaluation of the Midbrain in Parkinson's Disease

To the Editor.—We commend the investigation by Huber et al[1] of midbrain pars compacta size in Parkinson's disease (PD) using magnetic resonance imaging (MRI). The authors have stimulated interest in an important area of new research, namely the use of MRI to correlate anatomic finding in vivo with clinical disease. Their detailed attention to the MRI methodology adds credence to their findings. However, methodological issues related to the composition and selection of the control group need to be considered carefully and the design of the present study illustrates some of the difficulties frequently encountered.

The authors have not reported the range and mean (±SD) age for the mild and moderate/severe PD groups as well as the standard deviation for age in the control and PD groups. We are concerned that the group of mild PD patients may have been significantly younger than the control subjects. Age may have an effect on pars compacta size independent of the measured clinical variable (ie, severity of PD). McGeer et al[2] have reported a significant age-related loss of substantia nigra neurons between the ages of 20 and 80 years. We have recently documented in 36 normal volunteer subjects that the cross-sectional area of the midbrain (measured on sagittal MRI) declines significantly between the age of 26 and 79 years, and that this decline is particularly prominent in subjects over 60 years (submitted for publication). If the mild PD group was younger than the control group, it would be of interest to know whether age effects obscured potential differences in pars compacta size.

Second, the authors have not mentioned the male/female composition of the PD and control groups (all control subjects were spouses of patients). The higher prevalence of PD in males may have resulted in a higher number of female control subjects. It is of interest that, in our study (referred to above), the age-related decline in midbrain area was more prominent in men than in women, though we did not measure pars compacta size. In addition, it is not known whether the greater age-related mortality from PD in males reflects a greater susceptibility to pars compacta degeneration in male subjects.

It is of interest that the first MRI study of pars compacta size in PD[3] found very little overlap between control and PD groups, whereas the two subsequent studies[1,4] have found a much greater overlap. Differences in control groups and a wide variation in pars compacta size in normal subjects may partly explain these discrepancies. In our study, midbrain dimensions varied almost threefold in normal volunteer subjects between the ages of 26 and 79.

These studies highlight the importance of strictly controlling for age and gender in morphometric studies of the midbrain, though the logistics of volunteer recruitment often preclude such an ideal study design. As the authors point out, inadequate normative data, as well as an apparent overlap between PD and control values, precludes the use of MRI criteria (such as pars compacta size or asymmetry) as reliable diagnostic markers for PD at present. Continued MRI studies of brain structural changes in normal aging and in PD remain essential to resolve these issues.

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1. Huber SJ, Chakeres DW, Paulson GW, Khanna R. Magnetic resonance imaging in Parkinson's disease. *Arch Neurol.* 1990;47:735-737.
2. McGeer P, McGeer E, Suzuki J. Aging and extrapyramidal function. *Arch Neurol.* 1977;34:33-35.
3. Duguid JR, De La Paz R, DeGroot J. Magnetic resonance imaging of the midbrain in Parkinson's disease. *Ann Neurol.* 1986;20:744-747.
4. Braffman BH, Grossman RI, Goldberg HI, et al. MR imaging of Parkinson's disease with spin-echo and gradient-echo sequences. *AJNR.* 1988;9:1093-1099.

In Reply.—We appreciate the useful comments provided by Doraiswamy and associates. While we tried to make our report as methodologically sound as possible, they correctly point out that we did not fully evaluate the potential effects of age. The age (mean ± SD) for the mild Parkinson's disease group (61.4 ± 8.7), the moderate/severe Parkinson's disease group (66.1 ± 8.0), and the normal control subjects (68.4 ± 4.0) produced a difference among groups that just failed to reach statistical significance, $F(2,51) = 2.99$, $P < .06$. However, the relatively young age of the mild Parkinson's disease group does warrant an examination of the potential effects of age on our results. We performed an analysis of covariance, with age as the covariate, on both the average width and width difference on the first echo images. There was a significant difference among the groups for width average, $F(3,50) = 3.64$, $P < .02$, and width difference, $F(3,50) = 5.53$, $P < .002$. Post hoc comparisons indicated a significantly narrower average width in the moderate/severe Parkinson's disease group, and a greater left-to-right width difference in the mild Parkinson's disease group. This pattern is identical to our original analyses and suggests that age had no secondary effect on our results. The male/female composition of the mild Parkinson's disease group (11/5), the moderate/severe Parkinson's disease group (19/9), and the control group (5/5) was not significantly different, $\chi^2 = 1.2$. Thus, it is unlikely that sex had an effect on our results.

At the present time, magnetic resonance imaging measures do not provide reliable diagnostic information for the individual patient due to qualitative overlap with normal control subjects. While asymmetry in width does appear to be most evident quantitatively in the early stages of Parkinson's disease, advances with further research will depend on adherence to strict methodology. The issues raised by Doraiswamy and associates are important in this regard.

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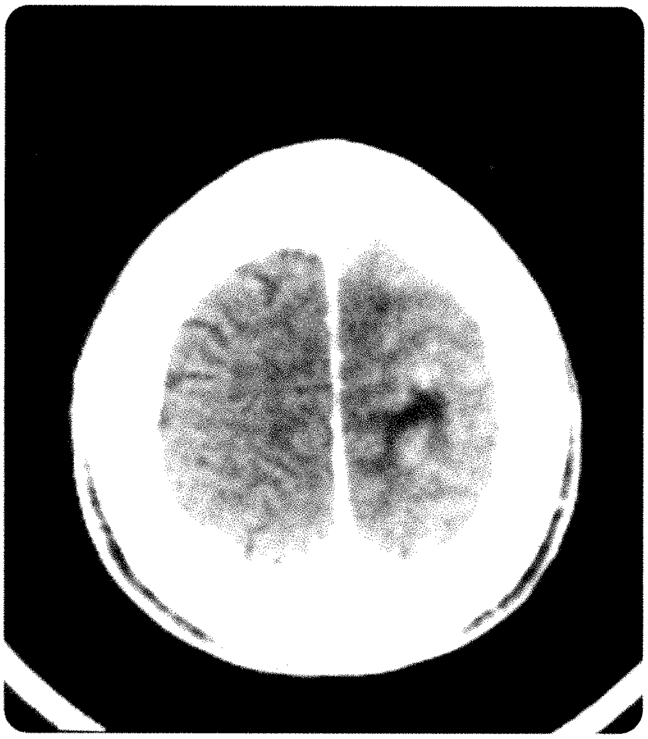
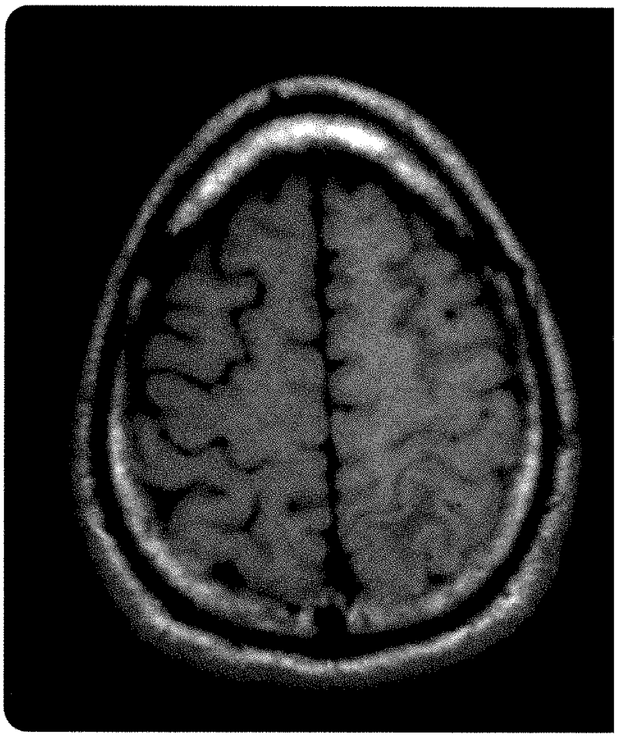


Contrast CT scan shows an area of low attenuation in the left parietal lobe. A questionable focus of contrast is seen, but this may represent cerebral cortex.

Images courtesy of Michael R. Ross, MD, Stanford University Medical Center, Stanford, California

Then MRI.



T1-weighted (TR 800/TE 20) unenhanced MR image, obtained with a 1.5-T imager, shows subcortical hypointensity in the lef posterior parietal lobe. The surrounding sulci appear to be compressed, but a mass is not clearly appreciated.

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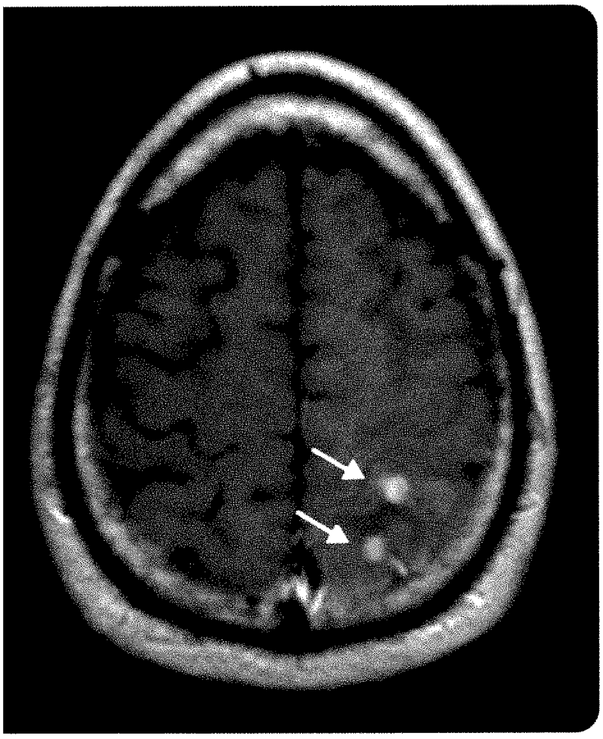
AND CONTRAST.

ow, *Magnevist*®-
nhanced MRI lets
ou see even more.



weighted (TR 800/TE 20) image enhanced with
AGNEVIST® injection reveals two discrete nodules
rows). This nodular enhancement is highly
ggestive of a primary brain tumor, which was
nfirmed upon biopsy to be an astrocytoma.

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

NOTHING LOCATES LESIONS BETTER

Please see brief summary of prescribing information for
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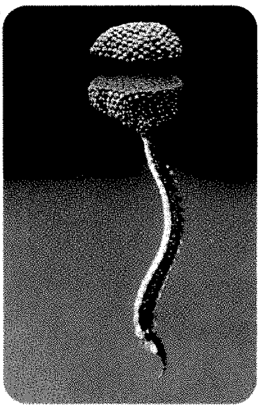

Well tolerated[1] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCE: 1. Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the. spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 µg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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Special Article

Compensatory Mechanisms in Degenerative Neurologic Diseases

Insights From Parkinsonism

Donald B. Calne, DM, Michael J. Zigmond, PhD

• In animal models of parkinsonism, the ability to lose a substantial proportion of dopaminergic neurons without behavioral deficits does not derive from other systems taking over function of the dopaminergic pathway. The surviving nigrostriatal projection increases both the rate of synthesis and the release of dopamine, as compensatory adjustments. This capacity allows at least a fivefold rise in dopamine delivery per neuron, and this enhancement is potentiated further by receptor up-regulation. Decreased reuptake, due to loss of nerve endings, may also lead to augmented occupancy of dopamine receptors, and so constitute yet another compensatory mechanism. In humans, positron emission tomography has revealed subclinical impairment of the dopaminergic nigrostriatal pathway in subjects at risk for parkinsonism caused by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine and Lytico-Bodig (the amyotrophic lateral sclerosis–parkinsonism dementia complex of Guam). However, the separation of patients with clinically overt idiopathic parkinsonism from controls is less marked in vivo (by positron emission tomography) than in postmortem analysis (by neurochemical assay). This disparity may be attributable to the reduction in the number of nigrostriatal nerve endings, leading, in vivo, to a relative increase of extracellular dopamine because active reuptake into the nerve endings is an important mechanism for removing dopamine from the synaptic cleft. In contrast, in a postmortem setting, dopamine that is not sequestered in the storage vesicles of nerve endings is readily available for biochemical degradation during the interval between death and brain analysis. Finally, it is also possible that differences may derive, in part, from dissimilar kinetic systems for handling exogenous and endogenous levodopa.

(*Arch Neurol.* 1991;48:361-363)

In seeking the cause of a degenerative disease, a first stage is the development of a conceptual model of pathogenesis. To formulate such a model, it is desirable to have information on the neurobiological adjustments that take place in the nervous system when some neurons have died and others are attempting to compensate and to maintain function. The most extensively studied pathway in this context is the dopaminergic component of the nigrostriatal bundle, and for this system, relevant animal observations can be correlated with phenomena observed in idiopathic parkinsonism.[1,2] In addition, since the dopaminergic cells of the zona compacta of the substantia nigra are selectively vulnerable to attrition with normal aging,[3] exploration of compensatory adjustments in these neurons should contribute to the elucidation of neurologic senescence. Thus, in this review we focus on animal and human studies of adaptations to lesions of nigrostriatal dopamine neurons.

ANIMAL STUDIES

6-Hydroxydopamine is a highly electroactive molecule that is concentrated by high-affinity transport systems of catecholaminergic neurons, particularly in the nerve terminals. Subsequent oxidation of this molecule produces highly toxic products, with resulting degeneration.[4] Injection of 6-hydroxydopamine into the brain of many experimental animals, either via the cerebrospinal fluid or directly along the nigrostriatal bundle, results in the death of dopaminergic neurons. The extent of the lesion depends on route of administration, dosage, and pharmacologic pretreatment.[1]

Gross behavioral changes do not occur following the administration of 6-hydroxydopamine unless the destruction of the nigrostriatal bundle is almost complete, and even then, the deficits are often transient.[1] Electrolytic lesions of the nigrostriatal system may also result in neurologic impairments that improve spontaneously,[5,6] and the same has been reported following administration of the toxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine to subhuman primates.[4]

The ability to undergo major loss of dopaminergic cells without clinical effects and the spontaneous improvement that commonly occurs when the lesions are severe enough to induce initial behavioral deficits do not reflect a transfer

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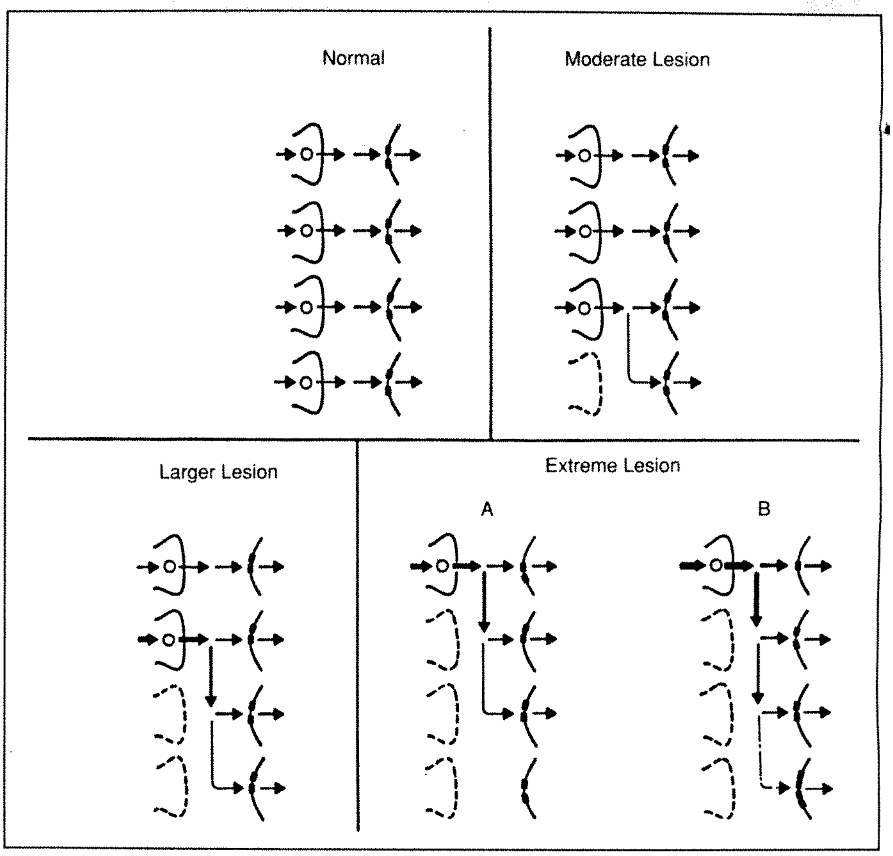
of function from the nigrostriatal bundle to other pathways. Neurologic deficits can readily be reestablished in lesioned animals by pharmacologic manipulations that compromise dopaminergic function still further. Indeed, lesioned animals are supersensitive to such treatments. Moreover, a minimal number of dopamine neurons must survive the lesion for recovery to occur.[6] These observations suggest the continued importance of the remaining elements of the nigrostriatal bundle.

The relation between size of an experimental lesion and neurologic deficit does not appear to derive from simple redundancy in the nigrostriatal system. The dopamine neurons that are spared by the injury have been shown to increase their synthesis and release of transmitter, suggesting an active, compensatory elevation in their functional activity.[7-9] The impact of this hyperactivity is augmented by the loss of sites for dopamine inactivation by reuptake due to degeneration of neighboring dopaminergic terminals[8,9] and, after extensive lesions, by an increase in the number of postsynaptic dopamine receptors[10] (Figure). Indeed, experiments have suggested that after partial nigrostriatal lesions, surviving dopaminergic neurons can increase their capacity to deliver transmitter by at least fivefold, and that the impact of this dopamine can be increased still further by receptor up-regulation. Taken together, these mechanisms may allow each surviving nigrostriatal neuron to compensate for the death of many similar cells before any functional deficit would be expected. Experimental observations at both the behavioral and the cellular levels are consistent with this prediction, and studies of damage to other monoaminergic systems in the brain and the periphery indicate that the capacity for such adaptation is widespread.[1]

It is possible that these compensatory processes exact a toll, however. The greatly enhanced turnover of dopamine could lead to the accumulation of toxic by-products of dopamine oxidation similar to those formed by 6-hydroxydopamine, thereby contributing to the ultimate degeneration of surviving elements of the nigrostriatal bundle. Furthermore, comparable toxic substances could accumulate in the extracellular space as a result of impaired removal of dopamine from the synaptic cleft consequent on loss of the nerve endings that possess an active reuptake mechanism. This vicious circle would generate more injury, to both dopaminergic and nondopaminergic cellular components.



A model for compensatory changes after lesions of the nigrostriatal bundle (from Zigmond and Stricker[1]). Top left, Under normal conditions synaptic transmission takes place with relatively little interaction between neighboring synapses. In addition, some synapses may be inactive. Top right, Moderate lesions have little or no functional impact for one or more reasons. Transmitter released at one synapse may act at a denervated site owing to the loss of inactivation via high-affinity uptake in that region (shown). There may also be some redundancy in the intact system, and previously silent synapses may become active (not shown). Bottom left, A larger lesion may require an increase in the synthesis and release of dopamine to keep postsynaptic function under dopaminergic control. A rise in the production of dopamine, together with the loss of high-affinity uptake sites, would result in a further increase in the field of influence of residual dopamine neurons (shown) and/or an increase in the postsynaptic response of innervated sites (not shown). Bottom right, After still larger lesions, rapid compensatory processes would be inadequate to restore function immediately. As a result, transmission would initially fail (A). However, a delayed compensation and recovery of function may occur (B). These additional compensations could include a gradual increase in the availability of tyrosine hydroxylase enzyme, a rise in the number of postsynaptic dopamine receptors, and the growth of new dopaminergic terminals.

OBSERVATIONS ON HUMAN SUBJECTS

As in the case of the animal models, postmortem analyses have indicated that neurologic deficits do not appear in idiopathic parkinsonism until the loss of striatal dopamine exceeds about 80%.[11] Moreover, concurrent measurements of the dopamine metabolite homovanillic acid suggest that degeneration of the nigrostriatal bundle is accompanied by an increase in dopamine turnover in humans as in laboratory animals.[12] Observations with positron emission tomography (PET) also indicate the presence of a substantial loss of nigrostriatal nerve endings in patients with clinically overt parkinsonism.[13-15] It is of interest from the viewpoint of documenting the compensatory potential of the human nigrostriatal pathway that PET has revealed subclinical damage to the nigrostriatal system in subjects with an increased risk of developing certain forms of parkinsonism.[16,17]

Postmortem analysis and PET also show normal age-related trends that are similar to, but less severe than, the changes found in idiopathic parkinsonism.[18,19] With this background, it has been proposed that the appearance and progression of clinical parkinsonism might result from age-related decompensation of an old subclinical nigrostriatal lesion.[20,21]

Positron emmision tomographic studies support the notion that animal experiments are clinically relevant. Moreover, the observations on animals also facilitate interpretation of PET. Since its inception, a persistent paradox has obscured the interpretation of PET with fluorodopa. Whereas human postmortem analyses of brains have revealed marked differences between striatal dopamine concentrations in normal and parkinsonian subjects, in vivo studies with PET have yielded less striking separation. This conflict may be resolved by taking into account the finding that in animals with partial lesions of the nigrostriatal bundle, the removal of dopamine from the synaptic cleft is substantially impaired because the decreased number of dopaminergic nerve endings means that active reuptake is decreased. Thus, whereas the intracellular content of striatal fluorodopamine formed from the exogenous fluorodopa PET tracer would be reduced by lesions of the nigrostriatal bundle, the accumulation of extracellular fluorodopamine might be enhanced. These predictions have recently been confirmed by direct neurochemical measurements in 6-hydroxydopamine–lesioned animals treated with L-dopa.[22] Since PET cannot distinguish between intracellular and extracellular pools of labeled compounds, the technique can be expected to provide an index of the parkinsonian striatal deficit that is consistently closer to normal values than estimates obtained from postmortem studies. Furthermore, in the postmortem setting, dopamine that is not sequestered in the storage vesicles of nerve endings is more readily available for biochemical degradation during the interval between death and brain analysis. This is conducive to increasing the separation of neurochemical findings between patients with idiopathic parkinsonism and normal subjects. Finally, it is also possible that the difference may derive, in part, from dissimilar kinetic systems for handling exogenous and endogenous levodopa.

COMMENT

The considerable power of adaptive mechanisms in certain neural pathways has implications for the search for the pathogenesis of neurodegenerative disease. In the case of degeneration of the nigrostriatal dopamine neurons, substantial compensatory events may occur and could interfere with the detection of functional impairments for an extended period of time.

If a similar situation obtains in the other common neurodegenerative disorders, there may be a shared category of pathogenesis in which early causal events occur without recognition because compensatory mechanisms preclude clinical expression. Moreover, the compensatory activity may have long-term deleterious effects. Further analysis of the neurobiology of compensatory adjustments might allow the development of improved methods for the detection and treatment of a variety of neurologic disorders.

References

1. Zigmond MJ, Stricker EM. Animal models of parkinsonism using selective neurotoxins: clinical and basic implications. *Int Rev Neurobiol.* 1989;31:1-79.
2. Kopin IJ, Markey SP. MPTP toxicity: implications for research in Parkinson's disease. *Ann Rev Neurosci.* 1988;11:81-96.
3. McGeer EG. Neurotransmitter systems in aging and senile dementia. *Prog Neuropsychopharmacol Biol Psychiatry.* 1981;5:435-445.
4. Heikkila RE, Cohen G. Further studies on the generation of hydrogen peroxide by 6-hydroxydopamine: potentiation by ascorbic acid. *Mol Pharmacol.* 1972;8:241-248.
5. Teitelbaum P, Epstein AN. The lateral hypothalamic syndrome: recovery of feeding and drinking after lateral hypothalamic lesions. *Psychol Rev.* 1962;69:74-90.
6. Marshall JF, Richardson JS, Teitelbaum P. *J Comp Physiol Psychol.* 1974;87:808-830.
7. Hefti F, Melamed E, Wurtman RJ. Partial lesions of the nigrostriatal system in rat brain: biochemical characterization. *Brain Res.* 1980;195:123-137.
8. Zigmond MJ, Acheson AL, Stachowiak MK, Stricker EM. Neurochemical compensation after nigrostriatal bundle injury in an animal model of preclinical parkinsonism. *Arch Neurol.* 1984;41:856-861.
9. Snyder GL, Keller RW Jr, Zigmond MJ. Dopamine efflux from striatal slices after intracerebral 6-hydroxydopamine: evidence for compensatory hyperactivity of residual terminals. *J Pharmacol Exp Ther.* 1990;253:867-876.
10. Creese I, Snyder SH. Nigrostriatal lesions enhance striatal [^{3}H] spiroperidol binding. *Eur J Pharmacol.* 1979;56:277.
11. Bernheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington: clinical, morphological and neurochemical correlations. *J Neurol Sci.* 1973;20:415-455.
12. Hornykiewicz O, Kish SJ. Biochemical pathophysiology of Parkinson's disease. *Adv Neurol.* 1986;45:19-34.
13. Martin WRW, Calne DB. Imaging techniques and movement disorders. In: Marsden CD, Fahn JS, eds. *Movement Disorders 2.* Stoneham, Mass: Butterworths; 1987:4-16.
14. Garnett ES, Firnau G, Nahmias C. Dopamine visualized in the basal ganglia of living man. *Nature.* 1983;305:137-138.
15. Leenders KL. PET tracer studies of striatal dopaminergic function. In: Fahn S, Marsden CD, Calne DB, Goldstein M, eds. *Recent Developments in Parkinson's Disease.* New York, NY: Macmillan Publishing Co Inc; 1987:105-121.
16. Calne DB, Langston JW, Martin WRW, et al. Positron emission tomography after MPTP: observations relating to the cause of Parkinson's disease. *Nature.* 1985;317:246-248.
17. Snow B, Guttman M, Peppard RF, et al. Asymptomatic nigrostriatal lesions in five patients with Guamanian ALS. *Neurology.* 1989;39:399.
18. Martin WRW, Palmer MR, Patlak CS, Calne DB. Nigrostriatal function in humans studied with positron emission tomography. *Ann Neurol.* 1989;26:535-542.
19. Carlsson A, Winblad B. Influence of age and time interval between death and autopsy on dopamine and 3-methoxytyramine levels in human basal ganglia. *J Neural Transm.* 1976;38:271-276.
20. Calne DB, Langston JW. Aetiology of Parkinson's disease. *Lancet.* 1983;2:1457-1459.
21. Calne DB, Eisen A, McGeer E, Spencer P. Alzheimer's disease, Parkinson's disease, and motoneuron disease: abiotrophic interaction between ageing and environment? *Lancet.* 1986;2:1067-1070.
22. Abercrombie ED, Bonatz AE, Zigmond MJ. Effects of L-dopa on extracellular dopamine in striatum of normal and 6-hydroxydopamine–treated rats. *Brain Res.* 1990;525:36-44.

Original Contributions

Corpus Callosotomy for Intractable Seizures in the Pediatric Age Group

Richard E. Nordgren, MD; Alexander G. Reeves, MD; Adele C. Viguera; David W. Roberts, MD

• The results of corpus callosotomy in 18 patients 16 years old and younger are presented. Eighty-three percent of our patients have had a significant improvement from the surgery (a decrease in seizure frequency of greater than 80% or no longer having generalized atonic, tonic, or tonic-clonic seizures). The procedure seems to be well tolerated in young patients, and we have not noted a postoperative deterioration in behavior, memory, or language function in our patients. One of our patients died in status epilepticus 3 months after surgery. Nevertheless, we have not encountered any serious morbidity in our other patients. Corpus callosotomy can be considered for children with intractable seizures, especially when generalized atonic, tonic, or tonic-clonic (whether primary or secondary) seizures are the major seizure type.

(*Arch Neurol.* 1991;48:364-372)

Corpus callosotomy is becoming a more widely used procedure in the treatment of intractable epilepsy and has been carried out in many patients in the pediatric age group. However, there have been very few series that have reported results in children exclusively.[1-4] The purpose of this article is to present the results of callosotomy performed in 18 children 16 years old and younger at the Dartmouth-Hitchcock Medical Center, Hanover, NH, and to review the results of callosal sectioning in children from other series reported in the literature.

PATIENTS AND METHODS

Our patients have had diverse causes of their epilepsy, including neonatal complications, infantile spasms, porencephaly, viral encephalitis, acute infantile hemiplegia, Rasmussen's syndrome, and Sturge-Weber syndrome. Also, several patients have been diagnosed as having Lennox-Gastaut syndrome secondary to various causative factors. The indications for corpus callosotomy in our series were as follows: (1) medical intractability of seizures (at least 4 years of intractable seizures with the attempted use of all standard anticonvulsants); (2) seizure type potentially amenable to callosotomy (particularly generalized atonic, tonic, or tonic-clonic seizures); (3) potential functional benefit if improvement in seizure control is achieved; (4) no single epileptiform focus identified.

Potential cases were evaluated by history, physical examination, neuroimaging, electroencephalography (EEG), neuropsychological testing, and Wada test when feasible. Long-term video-EEG monitoring and magnetic resonance imaging scanning have been carried out on patients since 1987.

Patients in this series who were operated on between 1971 and 1980 have been included in previous reports.[5-7] Six of our patients have had a complete callosal section performed in one operation, three patients have had only an anterior callosotomy, while nine patients have had a two-stage complete callosotomy. Complete callosal section, early in the series, included division of the entire corpus callosum (together with the underlying hippocampal commissure, one fornix, and the anterior commissure[5]); anterior callosotomy included division of approximately the anterior two thirds of the callosum; and two-stage commissurotomy included division of the entire corpus callosum and hippocampal commissure.[8] While most patients with anterior section will also need the posterior third sectioned, we now stage the corpus callosum section to prevent the side effects of total section in those who may not need the entire operation. One patient who had evidence for predominantly posterior seizure activity had the posterior callosum sectioned first.

We have used the International Classification of Epileptic Seizures (ICES)[9] for our patients' seizures. Most of our patients have had their seizures classified by historical data, for we have had video-EEG monitoring available at our institution only since 1987 (Table 1). We have also used the ICES for 50 patients reviewed from the literature who were 16 years old or younger at the time of their surgery (Table 2).[1-4,10-16] We feel that there are adequate data to classify the 50 patients' seizures, although the clinical details of the seizures vary and often there is a very limited description of the seizures. In our classification, we have included generalized tonic and generalized tonic-clonic seizures together and focal myoclonic seizures with simple partial seizures.

RESULTS

Effect on Seizures

Of the 86 patients who have undergone corpus callosotomy at the Dartmouth-Hitchcock Medical Center, 18 have been 16 years old or younger at the time of surgery and have had greater than 2 years of follow-up. Table 1 summarizes the clinical data on these patients, while Table 2 summarizes clinical data on 50 patients from the literature who have undergone corpus callosotomy by age 16 years. Table 3 summarizes the results of our patients and the patients from the literature using frequency of all seizures for the two groups, and Table 4 summarizes the results of callosotomy by seizure type for the two groups.

As can be seen from Table 3, the majority of our patients have had a greater than 80% reduction in overall seizure frequency. Also, one patient in the "50% to 80% reduction" group and one patient in the "no significant change" group are no longer having incapacitating seizures and can be considered much improved in

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Table 1.—Results of Corpus Callosotomy in 18 Patients*

Patient No./Age, y/Sex	Clinical Data	Operation, Year	Complications, Postoperative Status	Seizure			Postoperative New Seizure		Overall Results†
					Frequency				
				Type	Preoperatively	Postoperatively	Type	Frequency	
1/9/M	L hemiparesis developed 5 d after DPT; seizures began at age 4 y	Complete, 1972	Postoperative aseptic meningitis, hydrocephalus, VP shunt; employed, graduated from high school	Atonic	Many/day	None	None	None	Seizure free
				GTC	Many/week	None			
2/16/M	Intracerebral bleeding at age 2 y; seizure onset at age 4 y; retarded	Complete, 1973	Retarded, no functional change	R simple partial →GTC	4-5/wk	Occasional	Complex partial	Several/day	No significant change
				R simple partial	5-10/d	1-3/d			
				Absence	Many/day	None			
				Atonic	Many/day	None			
3/15/M	Herpes at age 10 y, emergent R temporal lobectomy; mild L hemiparesis; in school; NP: verbal, 92; performance, 74; full scale, 82	Complete, 1975	Working	Complex partial	3-4/d	None	Simple partial	4-5/wk, no location	>80% reduction
				Complex partial→GTC	10/mo	Several first year, none since			
				Atonic	10/mo	None			
4/15/M	8-hour prolonged focal R-side seizure with fever as infant; seizures began at age 10 y; NP: verbal, 83; performance, 99; full scale, 89; behavior problems	Complete, 1976	Postoperative aseptic meningitis; working; noncompliant; R hemiparesis worse after episodes of R epilepsy partialis continua that occur only when noncompliant	Complex partial	Several/week	None	R simple partial	1/mo	>80% reduction
				GTC	Occasional	3 in first year, none since	R focal epilepsy partialis continua when noncompliant	Rare	
				Atonic	Occasional	None			
5/16/M	Mumps encephalitis at age 7 y; coma, 5 d; personality change after that; seizure onset at age 9 y; NP: verbal, 76; performance, 72; full scale, 72; severe violent behavior	Complete, 1976	Graduated from high school with special classes, vocational program; working on parents' farm; no violence	Complex partial	3-5/d	None	Simple partial	1/mo	>80% reduction
				GTC	Several/week	1/mo			
				Absence	Many/day	None			
6/16/F	R porencephaly, L hemiparesis; NP: verbal, 73; performance, 72; full scale, 71	PC, 1980; AC, 1980	Improvement in school work; NP: verbal, 81; performance, 83; full scale, 81	Absence	Several/day	1/d	. . .	. . .	>80% reduction
				Simple partial →GTC	Several/day	None			
7/15/M	Difficult birth, intraventricular hemorrhage; seizure onset at age 2 y; bilateral atrophy on computed tomography; retarded, severe behavior problem	AC, 1983	Behavior better and in school	Complex partial	1-2/d	<1/mo	R simple partial followed by fall to ground	<1/y	>80% reduction
				R simple partial	Several/day	None			
				GTC	Occasional	None			
8/14/F	Onset 5.5 mo prolonged febrile seizure; NP: verbal, 52; performance, 41; full scale, 45; very drowsy and ataxic on medication	AC, 1983; PC, 1984	Less drowsy, less ataxic	Absence	Many/day	None	Clusters of simple partial, R or L, only at night	Every few weeks	>80% reduction
				Complex partial	Many/week	None			
				GTC	Several/week	None			
				R or L simple partial→GTC	Many/week	None			

*L indicates left; R, right; DPT, diphtheria-pertussis-tetanus immunization; NP, neuropsychologic testing; PC, posterior callosotomy; AC, anterior callosotomy; GTC, generalized tonic-clonic; CSF, cerebrospinal fluid; RDS, respiratory distress syndrome; absence, generalized absence; and atonic, generalized atonic.

†No significant change indicates less than 50% reduction in total seizure frequency.

(Continued on p 366.)

Table 1.—Results of Corpus Callosotomy in 18 Patients*(cont)

Patient No./Age, y/Sex	Clinical Data	Operation, Year	Complications, Postoperative Status	Seizure			Postoperative New Seizure		Overall Results†
					Frequency				
				Type	Preoperatively	Postoperatively	Type	Frequency	
9/12/M	Seizure onset at age 5 y; partial L frontal lobectomy at age 12 y; path: gliosis, ?Rasmussen's syndrome; NP: verbal, 58; performance, 64; full scale, 57	AC, 1983; PC, 1984	Better in school, graduated from high school with special classes	Complex partial →GTC	3-5/d	None	R simple partial	Several/day	50%-80% reduction in seizure frequency, but no disabling seizures
				Atonic	Occasional	None	R simple partial with slump to ground	Occasional	
10/15/F	Birth cyanosis, seizure onset at age 1 y; ?Lennox-Gastaut syndrome; severely retarded	AC, 1983; PC, 1984	No change	Absence	Many/day	No change	. . .	. . .	No significant change
				GTC	5-10/wk	No change			
11/14/M	Generalized seizure with high fever at age 1 y; Lennox-Gastaut syndrome; NP: verbal, 60; performance, 51; full scale, 52	AC, 1984	In school; NP: verbal, 65; performance, 48; full scale, 52	Absence	Hundreds/day	None	L simple partial	1-2/d	>80% reduction
				Generalized myoclonic→thrown to ground	Many/week	None	R simple partial	Occasional	
				Atonic	Many/day	None	"Graceful" drop to floor	Occasional	
12/10/M	Normal until age 3 y; onset of "petit mal" and later multiple seizure types; ?Lennox-Gastaut syndrome; severely retarded; NP testing not possible	AC, 1984; PC, 1985	Starting to read, mild trouble carrying out simultaneous activities both hands	Absence	Many/day	Many/day	R simple partial	Rare	No reduction in overall seizure frequency, but not having devastating seizures
				GTC	Several/week	Rare			
				Generalized myoclonic with falling	Daily	None			
				Generalized myoclonic, no falling	2-3/wk	4-5/d			
13/7/F	Premature, RDS, neonatal seizures; retarded, not able to communicate; NP not testable	AC, 1984; PC, 1985	No change in functional status other than improved seizure control	Atonic	Many/day	None	. . .	. . .	>80% reduction
				Simple partial	200-300/d	0-10/d			
14/8/F	Onset of seizures at age 6 mo; R parietal cortical resection at age 3 y; computed tomography and magnetic resonance imaging: atrophy (generalized) and R parietal resection; L-sided hemiatrophy; thalassemia trait; severely retarded; frequent episodes of status epilepticus	Complete, 1985	1 mo postoperatively developed CSF leak; CSF drain and *Escherichia coli* meningitis; bone flap removed; aseptic meningitis, frequent seizures	R and L; simple partial	Many/day	Died in status epilepticus 3 mo after surgery	. . .	. . .	Deceased
				GTC	2-6/wk				
15/8/M	Sturge-Weber syndrome, R hemiparesis; seizures began at age 3 y; computed tomography: L calcification and hemiatrophy; IQ between 45 and 54; behavior problems	AC, 1985; PC, 1985	Behavior and functional status much improved	Generalized myoclonic with falling backward	4-5/d	None	. . .	. . .	>80% reduction
				R simple partial →GTC	Several/week	None			
				R simple partial	Several/day	Several/week			

Table 1.—Results of Corpus Callosotomy in 18 Patients* (cont)

Patient No./Age, y/Sex	Clinical Data	Operation, Year	Complications, Postoperative Status	Seizure			Postoperative New Seizure		Overall Results†
					Frequency				
				Type	Preoperatively	Postoperatively	Type	Frequency	
16/16/F	Prolonged febrile seizure; institutionalized; NP: verbal, 56; performance, 69; full scale, 59	AC, 1986	Improved behavior, living in group home	Absence	Many/day	Rare	R simple partial	10-20/mo	>80% reduction
				GTC	20-30 in a day several days/month	4-5/mo	L simple partial	1-2/mo	
				Atonic	Occasional	Rare (only when ill)			
17/16/M	Onset of infantile spasms with hypsarrhythmia at age 3 mo; severely retarded, L hemiparesis	AC, 1986, PC, 1987	More alert, improved behavior	Atonic	5-6/d	None	Simple partial with partial loss of postural tone	Several/week	>80% reduction
				GTC	Several/month	None			
				Focal myoclonic jerks	50-60/d	Few on awakening			
				Complex partial	Daily	Several/week			
18/13/F	Birth asphyxia; retarded; NP testing not possible; seizures began at age 6 y; computed tomography: hemiatrophy R side	AC, 1987; PC, 1987	More alert, improved behavior	Absence	Many/day	2-3/d perimenstrually	L simple partial	Several/day	>80% reduction
				Complex partial →GTC	1-2/d	1/mo without generalization			

regard to their quality of life.

Table 4 summarizes our results by seizure type, and, as can be seen, more incapacitating seizures were quite likely to improve after corpus callosotomy. Eighty percent of our patients and 71% of the patients reviewed with primary generalized tonic or tonic-clonic seizures had either a greater than 80% reduction or no seizures of this type postoperatively. All of our patients and 60% of the patients reviewed with secondary generalized seizures had at least an 80% reduction in the number of this type of seizure postoperatively. With seizures associated with a sudden fall to the ground (generalized atonic or generalized myoclonic with falling), 11 (92%) of 12 of our patients are no longer having this type of seizure, and one patient has had an 80% seizure reduction. In the reviewed patients, 11 (65%) of 17 are no onger having this type of seizure, while two (12%) have had a greater than 80% reduction. The frequency of generalized absence seizures and complex partial seizures without generalization have also improved postoperatively in most of our patients.

Simple partial seizures are the most common seizure type present after surgery. Fifteen of our patients have had simple partial or focal myoclonic seizures after surgery, and in nine of these patients, the focal seizures are a new phenomenon. One patient developed a new type of simple partial seizure after surgery with more intense manifestations than in his previous focal seizures (about once per month he has a partial seizure with slumping to the ground), and one patient developed more frequent simple partial seizures after surgery, but was no longer having generalized atonic or tonic-clonic seizures. While we have had one patient develop complex partial seizures as a new seizure type postoperatively, there have been no patients with generalized atonic, absence, or tonic-clonic seizures postoperatively who did not have this type of seizure prior to surgery.

EEG Changes

The EEG changes in our patients following surgery were similar to those reported in other series.[17,18] Fifteen of our patients had clearly synchronous bursts of epileptiform activity prior to surgery and after callosotomy; nine of these had no synchronous bursts noted on postoperative EEGs, four had a markedly decreased frequency of synchronous bursts, and two had no obvious decrease in the frequency of synchronous bursts. Seven of our patients had clearly demonstrated independent epileptiform discharges from either hemisphere prior to surgery. Postoperative EEGs in these patients demonstrated only unilateral discharges in four patients, two patients had no significant change in the independent discharges, and one patient had no independent unilateral discharges on postoperative EEGs. Usually there was no change noted in background activity after surgery. It is difficult to extrapolate too much from the above data, since the EEGs in most of our patients are not prolonged recordings and mostly interictal samplings. However, it is suggestive that in many of our patients the synchronous discharges in fact represent secondary bilateral synchrony and that the corpus callosum is important for the development of these bilateral discharges.

Behavioral Changes

Transient "mutism" and paresis of the nondominant leg have been a minimal and short-lived problem in patients who have had a two-stage procedure,[19] while more severe difficulties were seen in some of the earlier patients who underwent a complete section. Our patients have all adapted to the chronic right/left afferent disconnection that follows section of the posterior half of the callosum.

Neuropsychologic testing was attempted in all of our patients prior to surgery, and there were no patients who had a significant deterioration in the test scores postoperatively. We have not noted the development of new language problems as reported by oth-

Table 2.—Results of Callosotomy in 50 Reviewed Patients*

Patient No./Age, y	Seizure Type		Overall Results†	Comment‡	Etiology, Presence of Focal Findings
	Preoperatively	Postoperatively			
Van Wagenen and Herren[10]§					
4/10	GTC	Occasional "petit mal"	>80% reduction	. . .	L hemiparesis
6/16	GTC	GTC	No significant change	Partial section	. . .
10/14	Multiple types	Jacksonian until medication restarted	>80% reduction	. . .	CVA at age 2 y, L hemiparesis
Luessenhop et al[1]					
1/3	Simple partial→GTC	Occasional simple partial	>80% reduction	. . .	L hemiplegia
2/3	GTC	Occasional simple partial	>80% reduction	. . .	L hemiparesis
3/7	GTC Simple partial	Occasional simple partial	>80% reduction	. . .	Epilepsia partialis continua followed by L hemiparesis
4/4 mo	Simple partial→GTC	Simple partial→GTC	No significant change	. . .	. . .
Amacher[11]					
1/14	Simple partial-GTC Simple partial	None 75% reduction	>80% reduction	. . .	L hemiplegia, atrophy in R hemisphere
2/16	Major motor Atonic Simple partial	None 50% reduction 50% reduction	50%-80% reduction	50%-80% reduction, but no major seizures	Atrophy in R brain
3/16	GTC Atonic	90% reduction 100% reduction	>80% reduction	. . .	. . .
Geoffroy et al[2]‖					
1/16	Absence; GTC; myoclonic	Total seizures, 20/d preoperatively; 3 myoclonic/day postoperatively	>80% reduction	. . .	. . .
2/13	GTC 6/d	Occasional GTC, 1-2 simple partial/week	>80% reduction	. . .	. . .
3/10	Absence; myoclonic; atonic	Preoperative "petit mal status"; postoperative 3 myoclonic/day	>80% reduction	. . .	. . .
4/7	Atonic, 3/d	Simple partial, 3/wk	>80% reduction	. . .	. . .
5/5	Atonic Absence	Atonic, 20/d pre- and postoperatively	No significant change	. . .	. . .
6/6	GTC, 15/d	Atonic, 5/d	>80% reduction	. . .	. . .
7/16	Simple partial→tonic and tonic-clonic, 5/d	Atonic, 5/d	>80% reduction	. . .	. . .
8/10	GTC, 6/d	Simple partial, 1-2/d	>80% reduction	. . .	. . .
9/7	Atonic, every 5 min; GTC; absences	Simple partial, 1/d	>80% reduction	. . .	. . .
Gates et al[12]					
6/15	Complex partial	No change	No significant change	. . .	Primary CNS neuroblastoma with radiation necrosis
Lassonde et al[3]‖					
1/7	GTC, myoclonic, absence, akinetic; total, 5/d	Seizure free	0 seizures	. . .	. . .
2/10	Atonic; GTC, 4/d	"Minor nocturnal," 2-3/mo	>80% reduction	. . .	. . .
3/13	GTC and atonic, 15/d	Simple partial, 4-5/mo	>80% reduction	. . .	. . .
4/15	Complex partial and GTC, 8-10/d	Simple partial, 1/mo	>80% reduction	. . .	. . .
Garcia-Flores[13]¶					
1/6	Simple partial, GTC, myoclonic, 30/mo	73% reduction	50%-80% reduction	. . .	Keffler-Landau syndrome, L frontotemporal atrophy
2/7	Simple partial, GTC, complex partial, 35/mo	99.6% reduction	>80% reduction	Anterior section	. . .
3/9	Absence, atonic, simple partial, GTC, 40/mo	22% reduction	No significant change	Anterior section	Head trauma, Lennox-Gastaut syndrome

*GTC indicates generalized tonic-clonic; R, right; L, left; CVA, cerebrovascular accident; CNS, central nervous system; absence, generalized absence; and atonic, generalized atonic.

†No significant change indicates less than 50% reduction in seizure frequency.

‡Patients had either a total callosotomy or a two-stage procedure unless mentioned in "Comment" section.

§Series only has follow-up of a few months.

‖Series does not comment on lateralizing features.

¶Series does not comment on postoperative seizure type.

#Seizure frequency not listed; only % change.

Table 2.—Results of Callosotomy in 50 Reviewed Patients* (cont)

Patient No./Age, y	Seizure Type: Preoperatively	Seizure Type: Postoperatively	Overall Results†	Comment‡	Etiology, Presence of Focal findings
4/10	Simple partial, myoclonic, GTC, 100/mo	Seizure free	0 seizures		Keffler-Landau syndrome, L hemisphere atrophy
5/11	Myoclonic, atonic, GTC, 17/mo	Seizure free	0 seizures	Anterior section	Tuberous sclerosis
6/13	"Salaam," GTC, myoclonic, complex partial, 23/mo	No improvement	No significant change	Anterior section	Anoxic encephalopathy
Rappaport and Lerman[14]					
1/13	Absence, 200/d	No improvement	No significant change	Posterior section	L hemiparesis, R cortical atrophy
2/2	Simple partial, 8/d; GTC, 2-3/d	Focal, 2-3/mo	>80% reduction		Sturge-Weber syndrome, R hemiparesis
3/9	Simple partial, 2/d; GTC, 2/d	Seizure free	0 seizures	L frontal lobectomy followed by posterior callosotomy	R hemiparesis, L porencephaly
5/11	Simple partial, 3-5/d; GTC, 2/d	Simple partial, 4/mo	>80% reduction		Sturge-Weber syndrome, L hemiparesis
6/12	Atonic, 6/d	Atonic, 1-2/mo	>80% reduction	Anterior section	R hemiparesis, L cerebral atrophy
9/16	Atonic and GTC, 3-/4d	Seizure free	0 seizures	Anterior section	R frontoparietal atrophy
Spencer et al[15]					
5/15	Simple partial, 500/mo; complex partial, 20/mo; GTC, 10/mo	Simple partial, 10/mo	>80% reduction	Previous R temporal lobectomy, total section	L hemiparesis, R hemiatrophy
10/12	Simple partial, 20/mo; complex partial, 20/mo; GTC, 8/mo	Simple partial, 10/mo; complex partial, 10/mo; GTC, 20/mo	No significant change		L frontal encephalomalacia
11/15	Simple partial, 300/mo; complex partial, 200/mo; GTC, 30/mo	Simple partial, 10/mo; complex partial, 50/mo; GTC, none	50%-80% reduction		R hemiparesis, L hemiatrophy
20/5	Simple partial, 200/mo; complex partial, 100/mo; GTC, 30/mo	Simple partial, 200/mo; complex partial, 100/mo; GTC, none	No significant change	More intense partial seizures	L hemiparesis
Purves et al[16]#					
7/13	Simple partial; complex partial	Simple partial, >80% reduction; complex partial, >80% reduction	>80% reduction	Anterior section	L hemiparesis, R porencephaly
18/13	Complex partial (two types)	Complex partial, >80% reduction of one type, slight reduction of another type	50%-80% reduction	Anterior section	L incoordination
Makari et al[4]					
2/11	Simple partial →GTC, 75/mo; complex partial, 75/mo	Simple partial →GTC, 4/mo; complex partial, 30/mo	50%-80% reduction	Anterior section	
3/11	GTC, 120/mo; atonic, 600/mo	Simple partial, 90/mo	>80% reduction	Anterior section	Asphyxia, L hemiparesis
7/16	GTC, 1/mo; absence, 30/mo	Seizure free	0 seizures	Anterior section	Dysgenesis of corpus callosum
8/7	GTC, 30/mo; tonic, 150/mo	GTC, 30/mo; tonic, 150/mo	No significant change	Anterior section	
10/7	GTC, 60/mo; atonic, 90/mo	Simple partial, 90/mo	No significant change in overall frequency	Anterior section	R hemiparesis, L hemisphere atrophy
14/14	GTC, 30/mo; tonic, 30/mo	GTC, 30/mo; tonic, 30/mo	No significant change	Anterior section	
18/7	GTC, <1/mo; atonic, 600/mo	GTC,<1/mo	>80% reduction	Anterior section	R hemiparesis, L hemisphere atrophy
20/8	GTC, 6/mo; complex partial, 30/mo	GTC, 6/mo; complex partial, 3/mo	50%-80% reduction	Anterior section	

ers following surgery.[20] Also, none of our patients have had an increase in, or development of, violent behavior or other behavioral problems. Many patients have had a very marked improvement in their behavior and alertness after callosal sectioning, presumably on the basis of decreased seizures and lower levels of anticonvulsant medications.

COMMENT

Corpus callosotomy has been used for the treatment of intractable seizures since 1939, when Van Wagenen and Herren[10] first introduced the procedure. However, it was not until the 1970s that this procedure became widely used, and there have been very few reports limited to children. Our results in 18 patients have been quite similar to those reported in large series of patients of all ages. For comparison, we have reviewed the published series of patients and analyzed the results in 50 patients 16 years old or younger for whom there are sufficient data to determine the types of seizures occurring preoperatively and for whom there are also postoperative seizure data (Table 2). Except for a series by Van Wagenen and Herren, there have been follow-ups of at least 6 months in the reviewed cases.

Corpus callosotomy should not be expected to eliminate seizures (even though we have had one child and there were six children reported who are seizure free after callosotomy) but, rather, to ameliorate more disabling seizures. Analysis by seizure type gives a better indication as to the expected results of callosal sectioning, and our results and those of the patients reviewed demonstrate that callosotomy can dramatically reduce the frequency of more disabling seizures (generalized atonic, tonic, and tonic-clonic).

When considering corpus callosotomy as a means of seizure control for a patient with intractable epilepsy, one must determine whether the patient is having seizures of a type that are likely to respond to the surgery. Also, one must consider whether the clinical description of the seizure allows one to classify accurately patient's seizures. We have found that, even with video-EEG monitoring, it is not always possible to exactly classify patient's seizures. If, however, seizures are considered on the basis of the most obvious clinical feature during the actual seizure, one can use historical data or clinical observation of seizures for a classification that is clinically very useful when assessing whether the patient may or may not be a candidate for callosotomy. With this in mind, we have considered two groups of seizures on the basis of obvious outcome of the seizure, regardless of the classification using the ICES criteria. The first are brief seizures during which the patient has a sudden fall to the ground, either because of a loss of tone or because of a positive phenomena (ie, a myoclonic jerk). The second is the combined group of generalized tonic or tonic-clonic seizures, with focal or generalized onset. The exact mode of onset or exact clinical manifestations do not appear to be crucial when trying to categorize patient's seizures into these two groups, and we have found that the response to callosotomy is not appreciably different if one considers subgroups of the larger two groups.

Brief seizures with falls are devastating to patients, often resulting in injuries and restricting patients' ability to function independently. These seizures usually occur many times per day and are often the most refractory to control with anticonvulsants. Table 5 combines

Table 3.—Results of Callosotomy: Frequency of All Seizures

	No. (%)	
Postoperative Frequency	**Our Patients (N = 18)**	**Patients Reviewed (N = 50)**
Seizure free	1 (6)	6 (12)
>80% reduction	12 (67)	26 (52)
50%-80% reduction	1 (6)	6 (12)
No significant change	3 (17)	12 (24)
Deceased	1 (6)	None reported

Table 4.—Analysis of Results by Seizure Type

	Seizures						
	No. of Our Patients (Reviewed Patients)						
			Postoperative Reduction				
Type	**Present Preoperatively**	**Absent Postoperatively**	**>80%**	**50%-80%**	**<50%**	**Postoperative Increase**	**Inadequate Data to Quantify Postoperatively**
Generalized tonic or tonic-clonic	10 (38)	5 (24)	3 (3)	. . . (1)	2 (9)	. . . (1)	. . . (. . .)
Generalized atonic	9 (17)	8 (11)	1 (2)	. . . (2)	. . . (2)	. . . (. . .)	. . . (. . .)
Generalized absence	9 (8)	4 (5)	3 (. . .)	. . . (. . .)	2 (3)	. . . (. . .)	. . . (. . .)
Generalized myoclonic without falling	1 (7)	. . . (3)	. . . (. . .)	. . . (1)	. . . (1)	1* (. . .)	. . . (2)
Generalized myoclonic with falling	3 (0)	3 (. . .)	. . . (. . .)	. . . (. . .)	. . . (. . .)	. . . (. . .)	. . . (. . .)
Simple partial without generalization	6 (15)	1 (2)	3 (5)	1 (5)	1 (2)	. . . (. . .)	. . . (1)
Simple partial with generalization	4 (5)	3† (1)	1 (3)	. . . (. . .)	. . . (1)	. . . (. . .)	. . . (. . .)
Complex partial without generalization	6 (13)	4 (1)	1 (5)	1 (3)	. . . (4)	. . . (. . .)	. . . (. . .)
Complex partial with generalization	3 (0)	2 (. . .)	1 (. . .)	. . . (. . .)	. . . (. . .)	. . . (. . .)	. . . (. . .)

*Patient no longer having myoclonic seizure with falling postoperatively.

†Two patients had simple partial seizures without generalization postoperatively.

the results for brief seizures with a sudden fall to the ground (generalized atonic and myoclonic with falling) for our patients and the reported patients. These data would indicate that corpus callosotomy is an effective treatment for these types of seizures in that all of our patients have had at least an 80% reduction of these debilitating seizures (92% no longer having these types of seizures), while 76% of the patients reviewed have had at least an 80% reduction (65% no longer having these types of seizures).

Obviously, generalized tonic and generalized tonic-clonic seizures are also disabling to a patient. As noted above, it is often very difficult to tell on the basis of description whether these are primary generalized or secondary generalized seizures and, therefore, we have combined the results for all generalized major motor convulsions in Table 6. In our series, 15 (88%) of 17 patients have had at least an 80% or greater reduction of generalized tonic or tonic-clonic seizures, and, in the patients from the literature, 31 (69%) of 43 patients have had at least an 80% reduction in these seizures.

Both in our series of patients and in those reviewed, simple partial seizures were frequent following surgery (15 of our 18 patients) and, in nine of these patients, the focal seizures were a new type. One of our patients and one of the patients reviewed developed more intense focal seizures. Many generalized seizures were converted to focal seizures, but almost always the focal seizures were considered less disabling to the patient.

The above data indicate that corpus callosotomy is an effective procedure for the treatment of intractable generalized seizures in young patients. The data also show that many patients with complex partial seizures will improve. There has been a less predictable response for simple partial seizures, and many patients have had their generalized seizures converted to more focal seizures. In our series, we have had one patient who developed complex partial seizures as a new seizure type postoperatively and we have had no patients with persisting tonic or tonic-clonic generalized convulsions and akinetic or absence seizures who did not have this type of seizure preoperatively.

Our present approach is to carry out the callosal section as a two-stage procedure to spare patients the potential effects of total disconnection. If there has not been a significant improvement in seizure control after the first stage, completion of the section is performed. There have been series where only partial corpus callosotomy has been performed,[4,16] but it has been pointed out previously that there is more likely to be improvement in seizures after a complete section than after a partial section.[21] This has been our experience. Of our 12 patients who initially had a partial section (posterior section was performed first in one patient), three had significant improvement after the first stage and had no further surgery and nine patients had completion of their section because of no major improvement after the first stage. Of these nine patients, seven had significant improvement after the second stage was performed. In the reviewed patients, 19 have had only a partial section with an "excellent" response in nine patients (47%), while 23 (74%) of the 31 patients who had a total section (in one or two stages) had an "excellent" response. These data would strongly support the consideration for a second-stage procedure if the first stage has not been helpful in controlling seizures. We have not yet been able to predict which patients will only need a single procedure, using either clinical or EEG data.

Sectioning of the corpus callosum can result in several types of behavioral and psychologic problems postoperatively. Since we have been carrying out callosotomy as a two-stage procedure, we have not had the "acute disconnection syndrome" as a major problem postoperatively. Some of our patients have had a very mild and transient hemiparesis that usually has resolved in a few days, and we have not had any patients develop persistent mutism postoperatively. We have attempted neuropsychologic testing in all of our patients, but this has not been feasible in many of them who are too retarded to test. Since we have initiated Wada testing on our potential callosotomy patients, none of our young patients have demonstrated the ability to be reliably tested for language and memory function and, therefore, have not had this procedure performed. Nevertheless, none of our patients has developed new memory or speech problems postoperatively. We have not noted the psychologic deterioration found by Sass et al[20] in some of their patients. Less extensive neuropsychologic test batteries have been routinely conducted in our patients when compared with the series of Sass et al, so subtle changes may have been missed. In the 50 patients reviewed, there has been definite deterioration noted in speech, memory, language function, or behavior in only one patient (patient 11 in the series by Spencer et al[15] and Sass et al). This patient appears to have had a significant deterioration in speech, verbal memory, and right arm function postoperatively. He had a right hemiparesis and left cerebral hemiatrophy demonstrated by neuroimaging, but had right hand preference and right-hemisphere language dominance; memory function was demonstrated in the right hemisphere only.

There may be several reasons why these problems are not seen more frequently in young patients. While these may be present but not observed, it is more probable that the younger patients have had a high incidence of a severely compromised hemisphere at the time of surgery and, as a consequence, language and memory function has been unilateral. Also, the younger nervous system may be better able to accommodate to the changes resulting from callosotomy. Lassonde et al[3] were able to demonstrate in a small series that younger patients were less affected by complete callosal sectioning when

Table 5.—Results Combining Generalized Atonic and Myoclonic Seizures With Falling to the Ground

Postoperative Frequency	Our Patients (N = 12)	Patients Reviewed (N = 17)
No seizures of this type postoperatively	11	11
>80% reduction	1	2
50%-80% reduction	0	2
No significant change	0	2

Table 6.—Results Combining All Generalized Major Motor Convulsions

Postoperative Frequency	Our Patients (N = 17)	Patients Reviewed (N = 43)
No seizures of this type postoperatively	10	25
>80% reduction	5	6
50%-80% reduction	0	1
No significant change	2	10
Increased seizures postoperatively	0	1

tested for unilateral discrimination and interhemispheric transfer of tactile information. The authors speculated that younger children could use extra callosal connections for interhemispheric transfer of information. Nevertheless, hemispheric memory and language function should be elucidated in patients preoperatively, if at all possible, and the possible deleterious effects on motor, language, and speech functioning of callosotomy must be kept in mind, especially when there is no evidence for same hemisphere dominance for hand and speech function.[20]

In our series and others, patients who have had evidence for unilateral disease, either on clinical examination or with neuroimaging, have tended to have the best results from surgery,[1,14] while less predictable results have been obtained in patients with evidence of diffuse pathogenicity or causes such as infantile spasms, Lennox-Gastaut syndrome, and asphyxia. This is especially true when these patients are suffering from hundreds of seizures per month or having frequent episodes of status epilepticus (including our one patient who died in status epilepticus 3 months after the procedure). Of our eight patients with clear unilateral pathogenicity, one has been seizure free, six have had a greater than 80% reduction in their seizure frequency, and one patient has had a 50% to 80% reduction in seizure frequency. Six of the 10 patients with no clear unilateral pathogenicity have had a greater than 80% reduction in seizure frequency, three have had no significant change, and one patient has died in status epilepticus. Further study is necessary to define criteria that will select patients with severe diffuse pathologic findings who most likely will respond to the surgery.

Some authors have considered mental retardation a relative contraindication for callosotomy,[6,15] but our experience has not borne this out.

Callosotomy should be considered in young patients when generalized atonic, tonic, and tonic-clonic seizures are occurring frequently. The deleterious effects of frequent recurrent seizures and the possibility of "kindling" leading to more refractory seizure foci over the years[22] may add to the surgical rationale for early surgical intervention. Young patients appear to tolerate the procedure better than do older patients, and an improvement in control of the seizures will often improve their behavior and cognitive functioning.

References

1. Luessenhop AJ, de la Cruz TC, Fenichel GM. Surgical disconnection of the cerebral hemispheres for intractable seizures. *JAMA.* 1970;213:1630-1636.

2. Geoffroy G, Lassonde M, Delisle F, Decarie M. Corpus callosotomy for control of intractable epilepsy in children. *Neurology.* 1983;33:891-897.

3. Lassonde M, Sauerwein H, Geoffroy G, Decarie M. Effects of early and late transection of the corpus callosum in children. *Brain.* 1986;109:953-967.

4. Makari GS, Holmes GL, Murro AM, et al. Corpus callosotomy for the treatment of intractable epilepsy in children. *J Epilepsy.* 1989;2:1-7.

5. Wilson DH, Reeves AG, Gazzaniga MS. 'Central' commissurotomy for intractable generalized epilepsy: series two. *Neurology.* 1982;32:687-697.

6. Wilson DH, Reeves A, Gassaninga M, Culver C. Cerebral commissurotomy for control of intractable seizures. *Neurology.* 1977;27:708-715.

7. Wilson DH, Reeves A, Gazzaniga M. Division of the corpus callosum for uncontrollable epilepsy. *Neurology.* 1978;28:649-653.

8. Roberts DW. Section of the corpus callosum for epilepsy. In: Schmidek HH, Sweet WH, ed. *Operative Neurosurgical Techniques: Indications, Methods and Results.* New York, NY: Grune & Stratton; 1988:1243-1250.

9. Commission on Classification of Epilepsies and Epileptic Syndromes. Proposal for revised classification of epilepsies and epileptic syndromes. *Epilepsia.* 1989;30:389-399.

10. Van Wagenen WP, Herren RY. Surgical division of commissural pathways in the corpus callosum. *Arch Neurol Psychiatry.* 1940;44:740-759.

11. Amacher AL. Midline commissurotomy for the treatment of some cases of intractable epilepsy. *Child Brain.* 1976;2:54-58.

12. Gates JR, Rosenfeld WE, Maxwell RE, Lyons RE. Response of multiple seizure types to corpus callosum section. *Epilepsia.* 1987;28:28-34.

13. Garcia-Flores E. Corpus callosum section for patients with intractable epilepsy. *Appl Neurophysiol.* 1987;50:390-397.

14. Rappaport ZH, Lerman P. Corpus callosotomy in the treatment of secondary generalizing intractable epilepsy. *Acta Neurochir.* 1988;94:10-14.

15. Spencer SS, Spencer DD, Williamson PD, et al. Corpus callosotomy for epilepsy, I: seizure effects. *Neurology.* 1988;38:19-24.

16. Purves SJ, Wada JA, Woodhurst WB, et al. Results of anterior corpus callosum section in 24 patients with medically intractable seizures. *Neurology.* 1988;38:1194-1201.

17. Spencer SS, Spencer DD, Williamson PD, Mattson RH. Effects of corpus callosum section on secondary bilaterally synchronous interictal EEG discharges. *Neurology.* 1985;35:1689-1694.

18. Gates JR, Leppik IE, Yap J, Gumnit RJ. Corpus callosotomy: clinical and electroencephalographic effects. *Epilepsia.* 1984;25:308-316.

19. Ross MK, Reeves AG, Roberts DW. Postcommissurotomy mutism. *Ann Neurol.* 1984;16:114.

20. Sass KJ, Spencer DD, Spencer SS, et al. Corpus callosotomy for epilepsy, II: neurologic and neuropsychologic outcome. *Neurology.* 1988;38:24-28.

21. Spencer SS. Corpus callosum section and other disconnection procedures for medically intractable epilepsy. *Epilepsia.* 1988;29(suppl 2):S85-S99.

22. Morrell F. Varieties of human secondary epileptogenesis. *J Clin Neurophysiol.* 1989;6:227-275.

Intraputaminal Infusion of Nerve Growth Factor to Support Adrenal Medullary Autografts in Parkinson's Disease

One-Year Follow-up of First Clinical Trial

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• Experimental studies in rodents show that β–nerve growth factor can increase the survival, neurite outgrowth, and functional effect of grafts of adrenal chromaffin cells to the basal ganglia. We, therefore, have begun to investigate whether treatment with nerve growth factor might also increase the functional effect of autografts of adrenal medullary tissue in patients with Parkinson's disease. Previous studies have shown that stereotactic implantation of adrenal tissue pieces produces a transient functional improvement that lasts for a few months. This report describes a trial of grafting of adrenal chromaffin tissue into the putamen, supported by infusion of nerve growth factor. The patient is a 63-year-old woman with a 19-year history of Parkinson's disease, now complicated by on-off phenomena and drug-induced hyperkinesia, despite optimized medical management. The left adrenal gland was removed, and the medulla was dissected into 1- to 2-mm^3 pieces in a solution containing nerve growth factor purified from mouse submandibular gland. Pieces were implanted in six tracts 3 to 4 mm from a previously placed cannula in the left putamen. Through the cannula, nerve growth factor was infused for 23 days for a total dose of 3.3 mg. Clinical assessment consisted of global ratings for rigidity and/or hypokinesia and for drug-induced hyperkinesia. Measures of gait and fine-motor control were also made. The motor readiness potential and auditory evoked potentials were recorded. The patient underwent follow-up closely for 4 months before and 13 months after grafting. She experienced no ill effects from any of the procedures, and antibodies to murine nerve growth factor, which closely resembles human nerve growth factor in amino acid sequence, did not develop. In the first postoperative month, she had a marked decrease in rigidity on the right side and a decrease in hyperkinesia. As with other patients with adrenal grafts but without nerve growth factor support, this improvement diminished during the second month. However, unlike these previous patients, our patient continued a slower phase of improvement that appears to have extended for at least the next 11 months. This course of improvement can be seen in the scores from global ratings of hypokinesia and/or rigidity, as well as amplitude of the motor-readiness potential. In addition, there was a tendency toward a decrease in the number of steps she needed to reverse direction while walking. There was no change in scores for hyperkinesia, speed of walking, or tests of fine motor control. From this single-patient study, it is not possible to draw conclusions about the mechanism of therapeutic effect or the eventual clinical utility of this approach. It seems, however, that nerve growth factor treatment may be safe in human beings and that it may prolong the effect of adrenal chromaffin grafts, consistent with earlier basic science findings.

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Extensive evidence accumulated from basic laboratory investigation on neuronal transplantation suggests that various sources of catecholamine-containing cells might provide a functional substitute for degenerating substantia nigra neurons in patients with Parkinson's disease.[1-6] Experimental data in rodents suggested that both fetal substantia nigra neurons[7,8] and adult chromaffin cells from adrenal medulla[9] might have such potential. However, fetal substantia nigra neurons appear to produce their functional effects in denervated rat caudate by forming a new dopaminergic innervation, whereas adrenal chromaffin cells synthesize and release dopamine and noradrenaline to diffuse into the caudate, and do not form nerve fibers or synapses.[1,2] Because of the difficulties involved with fetal grafting, including the potential need for lifelong immunosuppression, adrenal tissue was chosen for the initial clinical trials.[10,11] This tissue source has the distinct advantage of being available as an autograft, ie, from the patient's own adrenal medulla. Stereotactic implantation of adrenal medullary cells into the putamen of patients with Parkinson's disease produces a decrease in several parkinsonian symptoms. These effects include immediate marked improvements lasting for a day or two, probably caused by acute release of large amounts of catecholamines from the grafts, as well as more subtle improvements, particularly in the "off" symptom phase, that last, at most, a few months. However, all changes generally disappear by 90 days.[12] To provide a longer-lasting effect, other approaches have been tried. Open neurosurgical implantation of large pieces of adrenal medulla into the caudate nucleus showed initial promise,[13] but further clinical trials were less encouraging, and the morbidity and mortality were greater than that experienced with stereotactic implantation.[14,15] Human fetal dopamine neuroblasts produce longer-lasting change,[16-18] which suggests that the fiber outgrowth from the graft may be critical for more prolonged therapeutic effect. However, the problems of immunosuppression, infection, and other disadvantages of the fetal tissue source remain.

Several ways in which the efficacy of chromaffin grafts might be increased are known (for further review, see reference 19). Perhaps the most straightforward and best supported by animal data[20-22] would be to infuse nerve growth factor into the grafted area for a period of time after grafting. When chromaffin tissue is implanted into the dopamine-denervated rat striatum, temporary

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nerve growth factor infusion has several, apparently permanent, beneficial effects. First, many more chromaffin cells survive. Second, many of these cells transform into neuronal phenotypes, so that the host striatum becomes innervated by a network of graft-derived catecholamine-containing nerve fibers. Third, long-term functional recovery is improved, as measured by a reduction in apomorphine-induced rotations 1 year after grafting.

In the present report, we describe a technique of growth factor administration to the brain and the results of the first attempt to support chromaffin autografts in a patient with severe Parkinson's disease by intraputaminal infusion of nerve growth factor during the first postoperative month. No negative effects could be ascribed to the nerve growth factor treatment. Parkinsonian symptoms gradually declined in this patient and, 1 year after cessation of nerve growth factor treatment, the scores on some clinical rating scales are still significantly better than those recorded preoperatively. We, therefore, conclude that the technique of using nerve growth factor support for stereotactically implanted chromaffin autografts represents a viable experimental approach for further investigation of grafting strategies in Parkinson's disease.

PATIENT AND METHODS

Selection Criteria

Our general inclusion criteria were as follows: The patient should be younger than 65 years of age and have severe hypokinesia as a major symptom. There should be no other confounding diseases or disabilities. The patient must also be psychologically stable and not demented. Finally, there must be a clear response to levodopa therapy, but inadequate relief of symptoms, such as the presence of on-off phenomena, in spite of an optimized drug regimen. Informed consent was obtained from the patient, and all procedures had been approved by the Ethical Committee of the Karolinska Institute, Stockholm, Sweden.

Patient History

This woman was 63 years old at the time of grafting and had a history of Parkinson's disease for 19 years. The patient did well on levodopa treatment for about 10 years, when on-off symptoms appeared. Despite more frequent and higher doses of levodopa, and the addition of bromocriptine, symptoms became progressively more disabling. During daytime, the symptoms changed rather randomly between severe hypokinesia and hyperkinesia, with the latter dominating. There were only brief periods (lasting some minutes) of relatively normal motor control in between. The patient was rated as being in stage 4 according to the scale of Hoehn and Yahr.[23] Apart from the symptoms of parkinsonism, the patient was neurologically normal as judged from a computed tomographic scan of the brain and was otherwise healthy.

During preoperative morning off symptom periods when the morning medications were omitted for recording of readiness and auditory evoked potentials, the patient was rigid and bedridden or confined to a wheelchair. She could not move from the wheelchair to the examination table and back without considerable assistance.

Study Design

The patient was brought to the hospital regularly for clinical tests for 4 months prior to the operation and was admitted to the hospital for a continuous stay 3 weeks before and 3 weeks after the operation. Her optimized drug regimen (levodopa, 600 ± 100 mg; bromocriptine, 35 mg; and amitriptyline, 75 mg; divided into 11 daily doses) was maintained essentially unchanged until 7 months postoperatively, when selegiline became available and was added. Clinical assessments of symptoms were carried out regularly by experienced examiners as described below. The test battery was based partly on our previous studies[10,12,17] and included clinical scoring of symptoms, walking tests, pegboard tests of fine motor control, and neurophysiological recordings of readiness and auditory-evoked potentials.

Nerve Growth Factor Preparation and Purification

β-Nerve growth factor was purified from 400 male mouse (NMRI, body weight >30 g) submandibular glands, as previously described.[24,25] Elution from the second column of CM-Sepharose was by a linear gradient of sodium chloride,[25,26] yielding a peak of highly purified β-nerve growth factor (Fig 1). The concentration of nerve growth factor was determined from the specific absorbance at 280 nm (1.6 at 1 mg/mL in a 1-cm cuvette). Identity and purification was further verified by electrophoresis in sodium dodecylsulfate on a gradient polyacrylamide gel, and by immunoblotting of similar gels (Fig 1).

Purified, biologically active nerve growth factor was dialyzed against Ringer's solution with glucose, sterile-filtered twice, and tested for sterility using official standard high-stringency conditions as required for injectable substances by the European Pharmacopeia. It was then packed in syringes provided by the pump manufacturer (see below). Filled syringes were kept at 8°C until use. The final concentration of nerve growth factor in the syringes used for infusion was 600 μg of β-nerve growth factor per milliliter in the Ringer's solution with glucose, corresponding to 60 000 biological units per milliliter. The rationale for the use of mouse nerve growth factor is presented in the discussion.

Bioassay of Nerve Growth Factor Activity

The biological activity of nerve growth factor was measured in a nerve fiber outgrowth assay with explanted sympathetic ganglia from the 9-day-old chick embryo. The dissected ganglia were explanted into a collagen matrix.[25,27] Details of the technique have recently been presented.[28] To determine activity, the purified mouse nerve growth factor was added in a series of twofold dilutions, with final concentrations ranging from 0 to 20 ng/L. The cultures were incubated at 37°C using 5% carbon dioxide and 92% relative humidity. After 1 to 2 days, the cultures were examined in an inverted microscope equipped for phase-contrast and dark-field illumination. Activity tests of the nerve growth factor preparation showed that 5 ng of nerve growth factor per milliliter evoked a dense circular fiber halo, regarded as corresponding to an activity of 1 biological unit. This was the case also after dialysis and sterilization (Fig 1). In addition, samples of nerve growth factor remaining in the tubing and in the dead volume of the syringes were analyzed after being recovered from the patient. There was no loss of biological activity in these samples, as shown by the serial dilutions.

Enzyme Immunoassay for Antibodies to Nerve Growth Factor

Blood was drawn preoperatively and 2, 4, and 10 weeks postoperatively to detect possible immunization against the infused mouse nerve growth factor. An immunoassay (enzyme immunoassay) for nerve growth factor antibodies (Fig 1) was designed based on principles described in detail elsewhere.[29] Immunoplates (96-well multidishes, Nunc, Copenhagen, Denmark) were coated with the purified mouse β-nerve growth factor (1 μg/mL) in 0.05 mol/L of carbonate buffer (pH, 9.6). Each well received 50 μL, and the dishes were incubated at 4°C overnight. The immunoplates were blocked for 1 hour at room temperature with 1% bovine serum albumin in the same buffer. After washing with TRIS-buffered saline (0.02 mol/L of TRIS hydrochloride, pH, 7.4; 0.5 mol/L of sodium chloride, containing 0.5% Tween 20), dilutions (10^{-2} to 10^{-11}) of serum from the patient (in TRIS-buffered saline with 0.05% Tween 20) were added for an overnight incubation at 4°C. The plates were then washed extensively at room temperature, before incubation with biotinylated antibodies to human IgG (0.5 μg/mL; Vector Laboratories, Burlingame, Calif) for 30 minutes. Finally, β-galactosidase conjugated to streptavidin (Bethesda Research Laboratories, Gaithersburg, Md) was added for 15 minutes at a dilution of 1:5000, and the plates were subsequently washed. To start the enzyme reaction, 100 μL of reaction[29] buffer was added to each microwell with 100 μL of 0.2 mmol/L of methylumbelliferyl-β-galactoside. The resulting methylumbelliferone (excitation wavelength, 365 nm; emission wavelength, 450 nm) was assayed in a microplate fluorometer (Microfluor, Dynatech, Burlington, Mass). The results were plotted as a function of the serum concentration.

Surgical and Neurosurgical Procedures

Preoperative workup included a computed tomographic scan of the abdomen that demonstrated two normal-sized adrenal glands. Plasma catecholamine concentrations were determined,[30] and the results showed normal basal levels of noradrenaline and adrenaline.

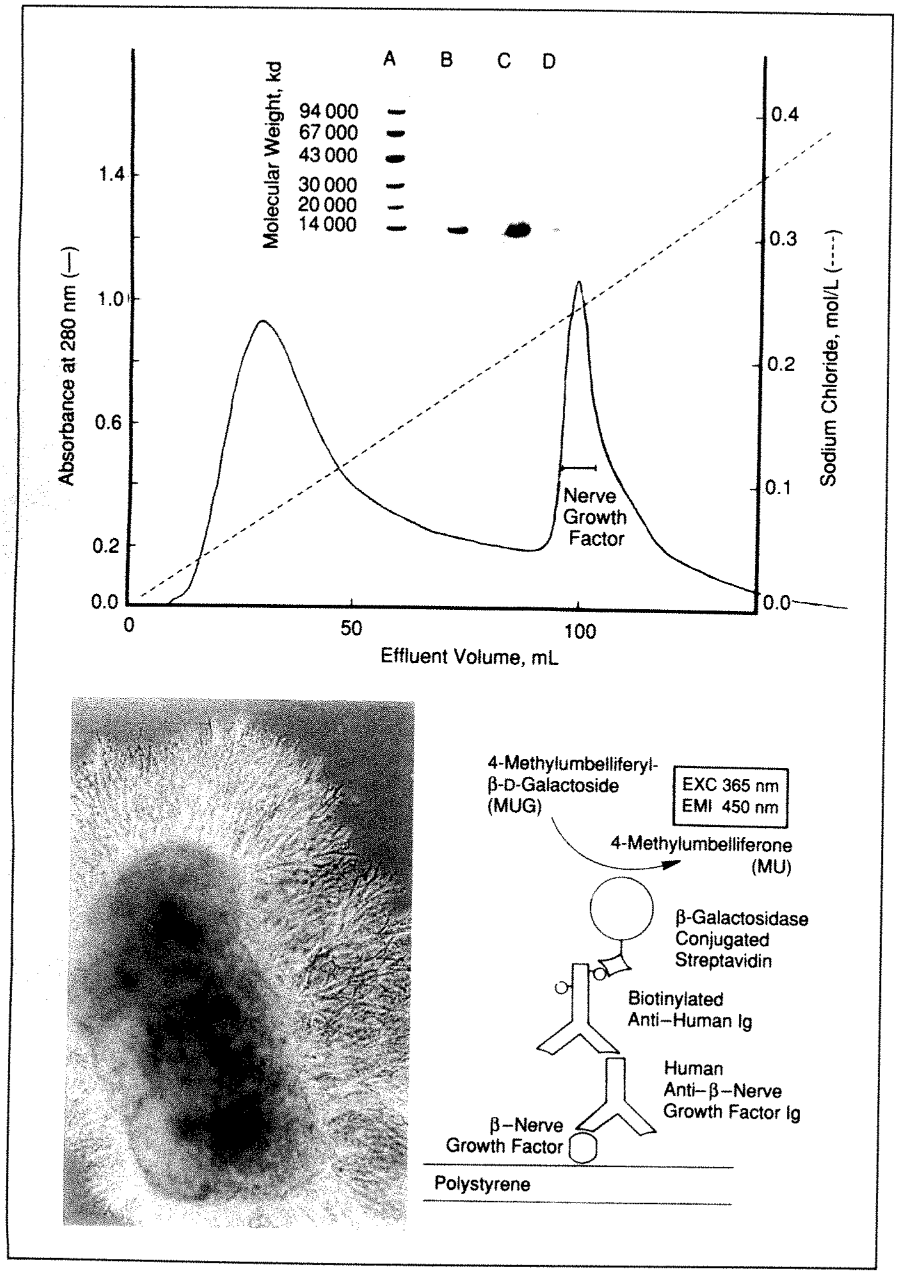

Fig 1.—Top, Elution profile of β–nerve growth factor from the second column of CM-Sepharose used in the purification.[24-26] The actual nerve growth factor peak (marked by the horizontal bar shown in this figure) was used for infusion to the patient described in this report. Inserts: A shows standard proteins of known molecular weight (14 000 to 94 000 kd) stained by coomassie blue after electrophoresis in sodium dodecylsulfate on a gradient polyacrylamide gel. B shows a similar experiment with nerve growth factor from the peak eluted by sodium chloride from the CM-Sepharose. Five micrograms of nerve growth factor protein was loaded in the lane. A main band (molecular weight, 14 000 kd) is apparent in this preparation in accordance with the molecular weight of 13 300 kd known from sequence data. C and D show immunoblots of β–nerve growth factor from gels similar to that shown in lane B. After transfer to nitrocellulose paper, the protein was incubated with antibodies raised to mouse β–nerve growth factor for subsequent detection of antibody binding by secondary biotinylated antibodies followed by incubation with iodine 125–streptavidin and x-ray autoradiography. The labeled bands again show a single major component with an apparent molecular weight of 14 000 kd. The lanes were loaded with 2 μg and 20 ng of nerve growth factor protein, respectively. Lower left, The biological activity of nerve growth factor given to the patient. After dialysis against Ringer's solution with glucose and subsequent sterilization by membrane filtration, a fraction of the nerve growth factor solution intended for infusion was diluted from 800 μg/mL to 12 ng/mL and incubated with a sympathetic ganglion from a chick embryo.[25,27,28] The activity of the nerve growth factor results in a massive nerve-fiber outgrowth after 1 day of culture as seen in this phase-contrast micrograph. Bottom right, The principle of the enzyme immunoassay used to test for the possible appearance of antibodies to the mouse β–nerve growth factor in the serum of the patient. A 96-well immunoplate was coated with the purified mouse β–nerve growth factor (1 μg/mL) and then blocked with serum bovine albumin. Different dilutions of serum samples taken before and at regular time points during and after the patient's treatment were then incubated in the wells. Possible antibodies binding to the coat of nerve growth factor were detected by incubation with biotinylated antibodies to human immunoglobulin followed by a conjugate of β–galactosidase and streptavidin. Resulting enzyme activities were measured by fluorometry of the product 4-methylumbelliferone. EXC indicates excitation wavelength; EMI, emission wavelength.

The neurosurgical procedures were essentially as previously used by us.[10,12] This time, however, six cylinders of adrenal medullary tissue were introduced, arranged around a central polyurethane catheter with an outer diameter of 1.4 mm, and used to infuse nerve growth factor. Under local anesthesia and using the stereotactic computed tomographic technique of Leksell and Jernberg,[31] coordinates for a target located centrally in the left putamen were determined. This target point was located 15-mm anterior and 5-mm superior to the midpoint of the intercommissural line, and 23-mm from the midsagittal plane (Fig 2).

Under general neuroleptic anesthesia, a burr hole was made in the left frontal region, close to the coronal suture. Via a few small skin incisions, the nerve growth factor–filled catheter was pulled from the region of the manubrium sterni to the burr hole (Fig 2). Using stereotactic technique, it was introduced to the predetermined target using a special cannulation technique[32] and secured to the edge of the burr hole. The incisions were temporarily sutured. The catheter was equipped with fine holes at the end and a sealed radio-opaque tip. The indwelling soft catheter was designed to compensate for any normal minor horizontal movements of the brain parenchyma relative to the skull. The assembly had a dead space of 0.8 mL and was filled with nerve growth factor solution. Because the effects of nerve growth factor were unknown, the left putamen was chosen for the target because the patient was left-handed. There were no preoperative side differences in her parkinsonian symptoms to contraindicate this decision.

The patient was next placed in the left lateral position. The left adrenal gland was chosen because it has a longer vein, which simplifies the adrenalectomy. The gland was removed using a lateral extraperitoneal approach, removing part of the 12th rib. A small rim of cortical tissue was left in situ. Since it has been shown that patients can maintain basal corticosteroid production from a resected gland,[33] this precaution should enable future removal of the right adrenal gland, if desirable. The adrenal gland was sectioned into slices from which medullary tissue was prepared. Pieces (1 to 2 mm^3) of adrenal medullary tissue, carefully freed from any adjacent cortical tissue, were collected in a solution consisting of 4 mL of

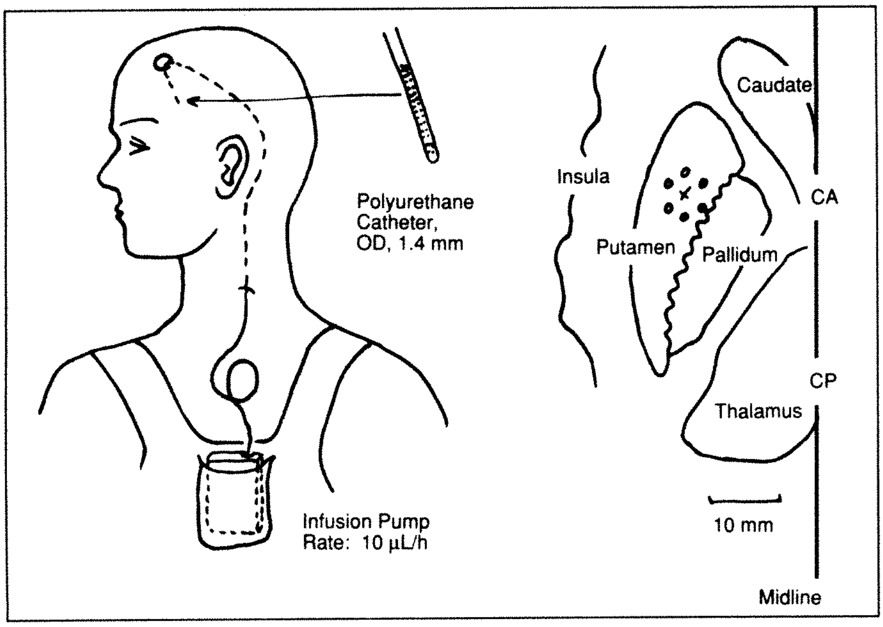

Fig 2.—At the right is depicted a schematic drawing of a horizontal section through the central nuclear complex of the human brain. The spatial arrangement in the putamen of the six adrenal medullary grafts (circles) and the nerve growth factor catheter (cross) is shown. The drawing to the left shows the design used for chronic intraputaminal infusion of nerve growth factor. The microinfusion pump for long-term nerve growth factor administration is percutaneously connected to a catheter, the tip of which is positioned in the putamen. OD indicates outside diameter; CA, anterior commissure; CP, posterior commissure.

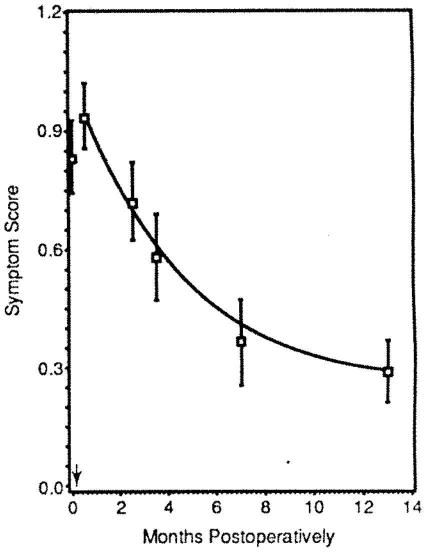

Fig 3.—Parkinsonian scores preoperatively and postoperatively. Each point represents the averaged scores from hourly scoring during a minimum of 5-day periods at the indicated times. The arrow indicates the time of operation and initiation of infusion of nerve growth factor. The mean scores are seen to decline exponentially postoperatively. Using approximate Wald tests, the curve is significantly lower than the preoperative mean 3.5 through 13 months postoperatively.

Ringer's solution with glucose, 2 mL of citrate plasma from the patient, and 0.5 mL of nerve growth factor solution containing 600 μg/mL of nerve growth factor. The implantation instrument previously described[10] was loaded six times with 13 to 15 pieces of adrenal medullary tissue in the nerve growth factor–containing solution. The pieces were deposited using six needle tracks, equidistant (3 to 4 mm) from the central implanted nerve growth factor–infusion cannula (Fig 2). The first implant was inserted 50 minutes after removing the adrenal gland, and the last, 114 minutes after adrenalectomy. Altogether, an estimated 85% of all available chromaffin tissue in the extirpated gland was used for implantation.

The pump (MiniMed Technologies, Sylmar, Calif) was connected to the tubing and affixed to the patient. Pumping at a rate of 10 μL/h was initiated 1.5 hours after the first implantation of adrenal medullary tissue. The infusion was carried out for 23 days by replacing the nerve growth factor–containing syringes every fourth to fifth day. The indwelling cannula and the subcutaneous tubing were removed 25 days after surgery.

Clinical Assessments

Rigidity/hypokinesia was evaluated using a scoring system for parkinsonian symptoms with the patient relaxed in the supine position, in a standing position, and walking, using the following scores: 0, absent; 1, slight; 2, moderate; and 3, severe. A similar scoring system was used to rate drug-induced hyperkinesia. In addition to the period before and after surgery (6 weeks), the patient was hospitalized and the scoring was carried out for approximately 5-day periods at intervals preoperatively and postoperatively. The scorings were made around the clock on the hour from 7 or 8 AM to 9 PM without interfering with the medication, generating a total of some 600 scores for symptoms and an equal number of scores for hyperkinesia at the time points indicated in Fig 3. The same team of experienced personnel (two physicians and four nurses) was responsible for all of the scoring throughout the study. The interrater reliability was checked operationally and repeatedly and found to be high. Tremor was observed only to a minor degree and intermittently in this patient, and was, therefore, not recorded. Gait was evaluated as the number of steps and time needed to walk 7 m and return. The number of steps needed to turn around was also recorded. The Mini-Mental State test[34] was used to evaluate possible signs of cognitive dysfunction on several occasions preoperatively and postoperatively.

Evoked Potentials

To provide information on central motor and sensory functions, averaged readiness and auditory evoked EEG potentials were recorded. The motor readiness potential consists of several components, one of which is a slow negative wave beginning about 1 second before a voluntary movement. This component is diminished in unmedicated patients with Parkinson's disease[35] and increases during the on-phase of levodopa treatment.[36] We have previously used the readiness potential to monitor effects of both adrenal medullary[12] and human fetal dopamine neuron[17] grafts to patients with Parkinson's disease.

Readiness and auditory evoked potentials were recorded with the patient in off-phase. For such recordings, the patient was instructed not to take any medication after 9 PM the night before, and the recordings were carried out the next morning prior to any medication. To record motor readiness potentials, the patient was supine and the torso was elevated 45°. A telegraph key was placed under one hand, and the patient was instructed to press the key slowly, self-pacing the movement at about 4-second intervals. The key was constructed so that a pulse was generated at the initiation of movement. Recordings were made at C_z, F_3, F_4, and 1-cm anterior to C_3 and C_4 in the International 10-20 System, referenced to the ipsilateral ear. A bipolar electro-oculographic recording was made from the lateral canthus and the superior orbit of the right eye. A bipolar electromyographic recording was made over the forearm flexor muscle group that contracted when the key was pressed. Electrical activity was amplified and filtered (0.01 to 30 Hz); the waveforms were digitized at 100 Hz and analyzed by computer. Fifty artifact-free trials were obtained for keypresses with each hand. The resulting averages were digitally smoothed by averaging data from each of three adjacent points. The motor readiness potential was quantified as the voltage 0.5 second before the movement, relative to the average potential 1.0 to 2.0 seconds before the movement.

Auditory evoked potentials were recorded from a vertex electrode employing a conditioning-testing paradigm. This paradigm uses paired stimuli to assess the gating of responses to sensory input. Subjects normally suppress the response to the second stimulus because of gating mechanisms activated during response to the first. The P50 wave is used as the target response because it is less affected by changes in the subject's attention. Decrease in suppression of the P50 wave with the conditioning-testing paradigm has been linked to increased catecholaminergic neurotransmission.[37] Such decreased suppression was observed following adrenal grafts in a previously studied set of patients.[12] For further details of the recording methods, refer to the article by Adler et al.[38]

Table 1.—Walking*

State	Parameter	Preoperative	Postoperative, mo 2-3	7	13
On	Time, s	14.4 ± 1.1 (16)	14.2 ± 0.4 (15)	13.7 ± 0.6 (3)	14.2 ± 0.4 (5)
	No. of steps	22.7 ± 1.5 (16)	22.9 ± 1.9 (15)	24 ± 2 (3)	23.6 ± 0.9 (5)
	No. of steps to turn	1.1 ± 0.3 (16)	1.1 ± 0.4 (15)	1.3 ± 0.6 (3)	2 ± 1 (5)
Off	Time, s	22.3 ± 3.6 (5)	22.1 ± 4.3 (7)	17 (1)	19 ± 2.8 (2)
	No. of steps	32.3 ± 1.5 (5)	39.1 ± 8.6 (7)	33 (1)	31.5 ± 6.4 (2)
	No. of steps to turn	5.8 ± 2.9 (5)	3.3 ± 0.8 (7)	3 (1)	3.5 ± 0.7 (2)

*Mean ± SD (No. of observations).

Statistics

Because of the variability of symptom intensity during the day, the clinical scores were analyzed by a two-way analysis of variance, with months before or after the operation and time of day as independent variables. The method of Grizzle et al[39] was used for the nonparametric analysis of categorical rating scores. The large numbers of observations for several of the measurements make possible meaningful analyses of the significance of change in this individual patient but do not allow statistical prediction about other future subjects.

RESULTS

Surgery

The operation was performed in May 1989 without complications. The patient was under general anesthesia for a total of 6 hours. There were no major changes in blood pressure during either adrenal removal or chromaffin tissue implantation in the brain. The patient woke up promptly after discontinuation of anesthesia. A postoperative computed tomographic scan showed the tip of the infusion catheter to be located correctly in the predetermined position in the center portion of the left medioputamen.

A computed tomographic scan 9 days after surgery showed that the tip of the nerve growth factor catheter had become dislocated 2.5-cm upward in the cannula tract sometime after the initial postoperative scan. Most probably, this was caused by hyperkinetic movements of the head and neck pulling on the catheter. The catheter was repositioned using stereotactic surgery under local anesthesia 12 days postoperatively. The repositioning was uneventful, and computed tomographic scans on the day of repositioning and several times afterward showed the tip of the catheter to be correctly positioned. Initially, there were slight signs of corticospinal tract dysfunction, consisting of an intermittently positive Babinski sign on the right side, but no paresis. This was most probably due to an edema, which developed around the catheter in the frontal lobe and which resolved during the next 2 to 3 months.

Postoperative Clinical Course

In the evening following surgery, deprived of medication since the night before, the patient was awake and mentally alert. There were clear-cut lateralized changes in her arms, such that there was only slight rigidity in her right arm, while her left arm was rigid in a cogwheel pattern. Such a lateralized difference did not exist before surgery. No pareses were noted. It was possible to begin reinstating her medication in the evening and, beginning the next day, to give her full medication.

The lateralized difference in rigidity was prominent during the first 14 postoperative days. Both the right arm and the right leg could be passively moved without rigidity, while cogwheel phenomena and rigidity were noticed on the left side. Notably, she had almost no hyperkinetic movements during this time. She was also more mobile in off than prior to surgery and was able to walk slowly.

The hyperkinesia gradually returned, beginning during the second postoperative month. Seven months postoperatively, it was decided to begin administering the selective monoamine oxidase–B inhibitor selegiline (Eldepryl, Farmos Group, Helsinki, Finland) to the patient, because of increasing evidence for its efficacy in other patients with Parkinson's disease. The effect of selegiline was initially dramatic, leading to a marked improvement of parkinsonian symptoms. Four months later, the improvement was less dramatic. When selegiline therapy was initiated, the levodopa medication was lowered by 350 mg/d because of increased hyperkinesia. Otherwise, no changes were made in the patient's medications, to permit comparisons between the preoperative and postoperative states. The Mini-Mental tests carried out on several occasions preoperatively and postoperatively did not show any cognitive dysfunction.

Ratings of Parkinsonian Symptoms

Analysis of variance of the global rating of rigidity/hyperkinesia showed a strongly significant ($P=.01$) effect of month of observation, which indicates that the patient's major parkinsonian symptoms had decreased following the operation (Fig 3). Hour of observation during the day was a nonsignificant factor ($P=.4$), and there was no interaction between hour and month.

The downward trend in Fig 3 was examined more closely. The differences between the six monthly means adjusted for time of day can be described in terms of a preoperative mean score, M, of 0.831 (±0.215) and a postoperative exponential decay curve, where

$$\text{Score} = a + (b - a)\, exp\, [(-0.693\ \text{Months} - 0.5)/c]$$

where $a = 0.261$ (±0.172) is the lower asymptote to which the score seems to be decaying, $b = 0.960$ (±0.087) is the maximum value observed 1 month after the operation, and $c = 3.023$ (±0.195) is the number of months after the operation at which the symptom score curve decayed halfway between the maximum at 0.5 month and the minimum M. The variables a, b, and c are all significantly different from zero at the .05 level. The fit of the preoperative and postoperative models are depicted in Fig 3. Using approximate Wald tests as discussed by Seber and Wild,[40] the curve is significantly lower ($P<.05$) than the preoperative mean 3.5 through 13 months after surgery.

Walking Tests

The time and number of steps needed to walk 7 m, make a 180° turn and return were repeatedly recorded preoperatively and postoperatively. As illustrated in Table 1, it appeared as if the time needed to carry out the test in off was decreased after the operation, while the number of steps did not change. There was a tendency for the number of steps required to make the 180° turn to decrease and remain less than preoperatively at the 13-month postoperative time point.

Pegboard Tests

The test records the time needed to place pegs in a board and, thus, is mainly a measurement of fine-motor control. As shown in Table 2, there was some decrease of the time to complete the test in off 7 and 13 months postoperatively, while there was a slight increase in the time to complete the test in on. No consistent changes were noted 2 to 3 months postoperatively. No major side effect differences in this test were observed.

Table 2.—Pegboard Test*

State	Side	Preoperative	Postoperative, mo 2-3	7	13
On	Right	74 ± 9 (17)	76 ± 5 (15)	88 ± 6 (6)	78 ± 16 (7)
	Left	68 ± 8 (17)	65 ± 8 (15)	83 ± 14 (6)	75 ± 19 (7)
Off	Right	111 ± 22 (9)	110 ± 41 (7)	97 ± 12 (3)	94 ± 16 (5)
	Left	100 ± 22 (9)	82 ± 16 (7)	89 ± 24 (3)	78 ± 10 (5)

*Time in seconds ± SD (No. of observations).

Readiness and Auditory Evoked Potentials

Recordings carried out in off at four occasions prior to surgery (2.5 months, 1.3 months, 0.7 months, and 3 days) showed the diminished readiness potential amplitude previously reported for unmedicated parkinsonian patients (Fig 4). Recordings made in the immediate postoperative period (6, 21, and 29 days) showed the marked increase in readiness potential amplitude seen in other patients who have received adrenal grafts.[12] The increase was present over both hemispheres and with movements of both the left and right hand. This increase was not noticeable in the 2.5-month postoperative recording. In the final recording, performed 13 months postoperatively, the readiness potential was moderately increased, compared with the preoperative records. The increase was greater over the left hemisphere and could only be elicited with movements of the right hand. These data are consistent with an improvement in function, localized to the left hemisphere. The time course of changes of the amplitude of the readiness potential recorded over the left hemisphere, as elicited by movements of the right hand, is illustrated in Fig 4. When the degree of readiness potential negativity was mapped over the patient's head, there was no side difference preoperatively. Thirteen months after surgery, there was clearly more negativity over the operated (left) than over the nonoperated hemisphere (Fig 4).

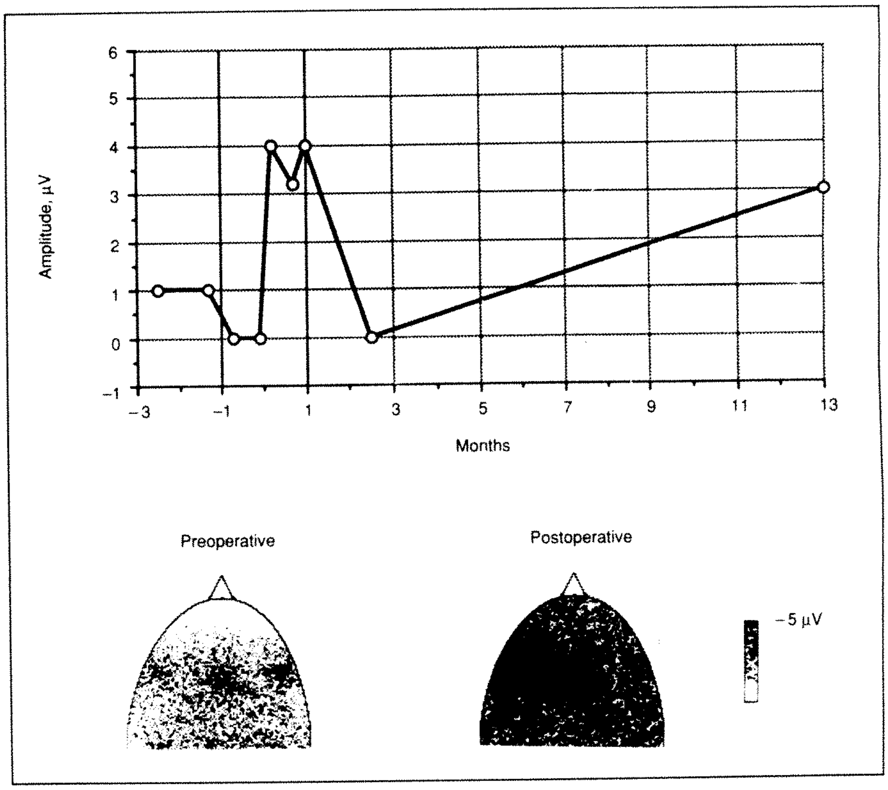

Fig 4.—Top, Readiness potentials recorded preoperatively and postoperatively from the left (operated) hemisphere, for right-hand movements. The potential is very low or absent at the four preoperative recordings and markedly increased during the first postoperative month. Although absent again at 2.5 months postoperatively, it is well above the preoperative average 13 months postoperatively. Below, Distribution maps of readiness potential negativity preoperatively (left) and 13 months postoperatively (right). Postoperatively, movements of the right hand cause a lateralized increase of negativity over the left (implanted) hemisphere.

The auditory evoked P50 potential showed normal amplitude, latency, and suppression in the preoperative period. A transient decrease in suppression in the first 3 postoperative months was noted, similar to that seen in the previously studied patients with adrenal grafts.[12] At the 13-month postoperative recording, the auditory evoked potentials were normal.

Nerve Growth Factor: Stability and Immunization Tests

Bioassay measurements of nerve growth factor activity in fluid remaining in used syringes as well as in the tubing, which was recovered when removing the tube and indwelling catheter, showed that storage at body temperature for several days did not decrease nerve growth factor activity at all. Measurements of the possible presence of anti–nerve growth factor antibodies in the patient's blood showed no significant differences between one sample taken preoperatively and three samples taken postoperatively. The largest difference between any one of the four samples was a factor of 1.8, which should be compared with a factor of approximately 10 000 between preimmune and postimmune serum samples typically seen when a rabbit is immunized with nerve growth factor.

COMMENT

This report is, to the best of our knowledge, the first documentation of administration of nerve growth factor to the human brain. A relatively large amount of purified mouse β–nerve growth factor was continuously infused into the putamen over a 3.5-week period. As far as our data indicate, this did not cause any negative effects either acutely or chronically. We, therefore, postulate that nerve growth factor administration in this way is a safe procedure.

The use of mouse nerve growth factor, currently the only nerve growth factor available in large enough quantities for such a trial, is based on the high degree of homology between nerve growth factor from various species. Thus, the amino acid sequence homology between mouse[41] and human[42,43] nerve growth factor is 90%. Of 118 amino acids, only 12 are different. Thus, mouse salivary β-nerve growth factor is equipotent in stimulating neurons from chick, mouse, and man. Mouse nerve growth factor has also been shown to stimulate human chromaffin cells in tissue culture.[44] By analogy, the homology between porcine and human insulin is 94%, a degree of similarity allowing porcine insulin to be used as a drug for human diabetes. Moreover, the use of human recombinant nerve growth factor, although preferable if it can be produced in quantity and purified, is no guarantee against immunization. For example, mice can be immunized with mouse nerve growth factor using the appropriate protocols (such as Freund's adjuvant) to generate good-quality anti–nerve growth factor antibodies.[45] The likelihood of immunization to a foreign or rare protein should, however, be much lower if the protein is injected into brain tissue. Indeed, an ultrasensitive immunoassay[29] could not detect signs of immunization following nerve growth factor infusion in the present case. Finally, in terms of the safety of the procedure, it is worth noting that adult laboratory animals in which very high titers of anti–nerve growth factor antibodies have been induced have no overt signs of disease.

It is well known that adult chromaffin cells in rodents can transform toward neuronal phenotypes following grafting[46] and that this transformation is induced by nerve growth factor.[20] Although such neuronal transformation does not appear to be necessary for adrenal grafts to have some beneficial effects in the rat model of Parkinson's disease (unilaterally 6-hydroxydopamine–denervated striatum),[20,47] nerve growth factor markedly increases the number of surviving chromaffin cells, induces neuronal transformation and nerve fiber production (see also reference 48), and increases the functional effects of the chromaffin grafts.[20] Such marked effects of exogenous nerve growth factor are probably best explained by the fact that the striatum normally contains very low levels of both nerve growth factor messenger RNA[49] and endogenous nerve growth factor protein.[50] The results with nerve growth factor–supported grafts seen in laboratory animals,[20] including more recent data suggesting that aged chromaffin tissue also responds to nerve growth factor[22] as well as a more detailed analysis of the nerve cell transformation of nerve growth factor–treated chromaffin cells,[21] form the basis for the present clinical study. Without nerve growth factor, the positive effects seen in patients given chromaffin tissue into the putamen and caudate appear to be approximately of the same magnitude and duration in man[12] as it is in rat.[20] Indeed, a chromaffin autograft, recovered postmortem 4 months after implantation into a patient with Parkinson's disease, revealed modest survival and scant tyrosine hydroxylase immunoreactivity paralleled by little clinical benefit.[51] In marked contrast, nerve growth factor support leads to more pronounced and long-lasting effects on motor behavior in both rats[48] and, as described here, man.

It has recently been suggested[52] that the positive effects of transplantation of fetal and chromaffin cells to dopamine-lesioned striata in rodents,[7-9] nonhuman primates,[53,54] and man[10,12,13,17] are due to nonspecific actions of the graft surgery. In terms of stereotactic implantations to man, the data in this communication argue against such a suggestion, since the addition of nerve growth factor changed the functional outcome after stereotactic implantations of chromaffin cells, compared with earlier results using the same surgical techniques.

The positive long-term changes in this patient are best documented in the statistical analysis of the global symptom scores. There were other indicators of the presence of longer-term changes, which were different in some regards from the effects observed in patients who had received adrenal grafts without nerve growth factor. Thus, the readiness potentials indicate long-lasting effects and suggest improvements of function over the left hemisphere. The auditory evoked potentials showed differences as well. The early postoperative loss of suppression of the P50 wave, seen in all of the patients who underwent an adrenal graft, including this one, suggests a massive release of catecholamines. The ensuing normalization of suppression, observed in this patient as well as in the patients who received fetal mesencephalic grafts, suggests that release is limited to the basal ganglia, perhaps because of more localized release and reuptake from newly formed nerve fiber terminals. It is also interesting that the patient showed an unusually positive response when selegiline treatment was initiated. This suggests that monoamine oxidase–B inhibition may increase the availability of catecholamines released by the chromaffin cell grafts.

Although the patient herself has not experienced any major improvements in activities of daily living, the significant long-term decrease in parkinsonian symptoms and the apparent absence of negative effects of nerve growth factor infusion described in this report suggest that chromaffin autografts, supported by temporary nerve growth factor infusion, should be investigated further.

In comparison with the open neurosurgical approach introduced by Madrazo et al,[13] stereotactic implantation appears to have several advantages. First and foremost, it enables implantation into the putamen. Second, it is less traumatic and, therefore, should carry fewer risks for the patient. In terms of efficacy, it is too early to draw any firm conclusions, but it is clear from the relatively large number of patients now treated by adrenal autografts implanted into the caudate[55-60] that the initially reported dramatic and sustained improvements have not been replicated[59,60] and that there is significant morbidity and/or mortality (eg, reference 58).

In comparison with implantation of fetal substantia nigra neurons obtained from aborted fetuses,[17,18] currently also under clinical trial in Parkinson's disease, the chromaffin alternative offers some advantages. First, there is no need to coordinate the grafting activities with the procurement of fetal brain tissue. Second, immunosuppression, currently believed by several groups to be necessary with fetal grafts,[17] is not needed with autografts. Third, it is possible that grafted dopamine neurons might be more susceptible to the disease process than would the grafted chromaffin cells. Several other factors that may be of potential importance also differ between the two procedures. The mesencephalic fetal brain tissue grafts by necessity contain several types of immature neurons other than dopamine neurons, as well as glial precursor cells. On the other hand, chromaffin cells secrete only small amounts of dopamine and larger amounts of noradrenaline. While, in the absence of high local concentrations of corticosteroids and after nerve growth factor–induced transformation, chromaffin cells may cease to produce adrenaline, it is not known to what extent other substances normally secreted by chromaffin cells (such as endorphins) are still synthesized, released, and influence the host brain.

Based mainly on studies of tyrosine hydroxylase immunoreactivity following dopaminergic lesions with methylphenyltetrahydropyridine (ie, MPTP), it has been suggested that adrenal medullary grafts may exert a trophic influence on remaining host dopamine terminals.[61] A similar effect has been described also in primates[62] and cannot be excluded in the present case. However, it does not readily explain the difference in duration of effects between our present nerve growth factor–supported case and our previous adrenal medullary implantations not supported by nerve growth factor. Indeed, studies in 60HDA-denervated rats that are so completely denervated that dopaminergic sprouting cannot occur prove that nerve growth factor–supported adrenal medullary grafts *can* reduce turning behavior without having to assume trophic effects and that these reductions are correlated to the amount of surviving cells and nerve fibers formed by the grafted cells.[48] Clearly, further work is needed to determine the relative role of directly graft-derived catecholamines vs graft-induced trophic effects on host neurons.

As presented elsewhere recently,[19] there are several ways in which the chromaffin autograft procedure might be improved in the future. Perhaps most important, it may become possible to increase the number of cells by treating dissociated chromaffin cells in culture with basic or acidic fibroblast growth factor in the presence of dexamethasone. This procedure induces mitosis, neuronal differentiation, and nerve growth factor dependence in immature rat chromaffin cells[63,64] and can also induce division in adult chromaffin cells. Thus, one could envision a two-step procedure in which chromaffin tissue is first removed from the patient. Cells would then be grown in culture to appropriate amounts and subsequently grafted back to the basal ganglia of the patient in the form of suspensions.

The recent discovery that nerve growth factor is a member of a family of closely related factors including brain-derived neurotrophic factor (ie, BDNF[65]) and neurotropin-3/hippocampal-derived neurotrophic factor (ie, NT-3/HDNF[66-69]), which are all synthesized by neurons in the brain,[70-72] opens new possibilities for treatments with combinations of grafts and/or growth factors in neurological disease. The present data are particularly relevant to Alzheimer's senile dementia, since they suggest that nerve growth factor might be safely administered for extended periods of time to the human brain, a strategy recently considered also for Alzheimer's disease (see, eg, Goedert et al[73]). In the latter case, based on animal experimentation, it has been speculated that nerve growth factor might counteract cholinergic deficits by exerting trophic effects on the ascending cholinergic projections to the hippocampus and cortex cerebri (see reference 74).

In conclusion, we have shown long-lasting positive effects of adrenal autografts supported initially by nerve growth factor infusion in a patient with severe Parkinson's disease. Although grafting strategies in Parkinson's disease only aim at compensating for the neuronal losses once they have occurred, they remain potentially important approaches for patients who have already lost substantia nigra neurons. Obviously, ways of preventing the degeneration of dopamine neurons, such as the current trials with monoamine oxidase-B inhibition or the identification of specific dopaminotropic factors, would be extremely important therapies once shown to be clinically effective. These complexities notwithstanding, among the alternative transplantation strategies, we believe that chromaffin autografts, placed stereotactically in the basal ganglia and supported by temporary nerve growth factor infusion, merits further scientific exploration on the basis of the present findings.

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References

1. Olson L. Grafting in the mammalian central nervous system: basic science with clinical promise. In: Magistretti P, ed. *Discussions in Neurosciences*. Geneva, Switzerland: FESN; 1988;5:1-73.

2. Olson L, Backlund E-O, Freed W, et al. Transplantation of monoamine-producing cell systems in oculo and intracranially: experiments in search of a treatment for Parkinson's disease. *Ann N Y Acad Sci*. 1985;457:105-126.

3. Freed W, Hoffer B, Olson L, Wyatt R. Transplantation of catecholamine-containing tissues to restore the functional capacity of the damaged nigrostriatal system. In: Sladek J Jr, Gash D, eds. *Neural Transplants: Development and Function*. New York, NY: Plenum Press; 1984:373-406.

4. Sladek J Jr, Gash D. Nerve-cell grafting in Parkinson's disease. *J Neurosurg*. 1988;68:337-351.

5. Lindvall O. Transplantation into the human brain: present status and future possibilities. *J Neurol Neurosurg Psychiatry*. 1989;126(suppl):39-54.

6. Gash D, Sladek J Jr. Neural transplantation: problems and prospects: Where do we go from here? *Brain Res Mol Brain Res*. 1989;5:1-7.

7. Perlow MJ, Freed WJ, Hoffer BJ, et al. Brain grafts reduce motor abnormalities produced by destruction of nigrostriatal dopamine system. *Science*. 1979;204:643-647.

8. Björklund A, Stenevi U. Reconstruction of the nigrostriatal dopamine pathway by intracerebral nigral transplants. *Brain Res*. 1979;177:555-560.

9. Freed W, Morihisa J, Spoor E, et al. Transplanted adrenal chromaffin cells in rat brain reduce lesion-induced rotational behaviour. *Nature*. 1981:292:351-352.

10. Backlund E-O, Granberg PO, Hamberger B, et al. Transplantation of adrenal medullary tissue to striatum in parkinsonism: first clinical trials. *J Neurosurg*. 1985;62:169-173.

11. Olson L, Backlund E-O, Sedvall G, et al. Intrastriatal chromaffin grafts in experimental and clinical parkinsonism: first impressions. In: Usdin E, Carlsson A, Dahlström A, Engel J, eds. *Catecholamines: Part C: Neuropharmacology and Central Nervous System: Therapeutic Aspects*. New York, NY: Alan R Liss Inc; 1984:195-201.

12. Lindvall O, Backlund E-O, Farde L, et al. Transplantation in Parkinson's disease: two cases of adrenal medullary grafts to the putamen. *Ann Neurol*. 1987;22:457-468.

13. Madrazo I, Drucker-Collín R, Díaz V, et al. Open microsurgical autograft of adrenal medulla to the right caudate nucleus in two patients with intractable Parkinson's disease. *N Engl J Med*. 1987;316:831-834.

14. Bakay R, Herring C. Central nervous system grafting in the treatment of parkinsonism. *Stereotact Funct Neurosurg*. 1989;53:1-20.

15. Goetz CG, Olanow CW, Koller WC, et al. Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. *N Engl J Med*. 1989;320:337-341.

16. Lindvall O, Rehncrona S, Gustaavii B, et al. Fetal dopamine-rich mesencephalic grafts in Parkinson's disease. *Lancet*. 1988;2:1483-1484.

17. Lindvall O, Rehncrona S, Brundin P, et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease: a detailed account of methodology and a 6-month follow-up. *Arch Neurol*. 1989;46:615-631.

18. Lindvall O, Brundin P, Widner H, et al. Grafts of fetal dopamine neurons survive and improve motor function in Parkinson's disease. *Science*. 1990;247:575-577.

19. Olson L, Strömberg I, Ebendal T, Seiger Å. Hoffer B. Grafting strategies in Parkinson's disease: the chromaffin alternative. In: Lindvall O, ed. *Fernström Symposia*. Amsterdam, the Netherlands: Elsevier Science Publishers. In press.

20. Strömberg I, Herrera-Marschitz M, Ungerstedt U, Ebendal T, Olson L. Chronic implants of chromaffin tissue into the dopamine-denervated striatum: effects of NGF on graft survival, fiber growth, and rotational behavior. *Exp Brain Res*. 1985;60:335-349.

21. Strömberg I, Hultgård-Nilsson A, Hedin U, Ebendal T. Fate of intraocular chromaffin cell suspensions: role of initial nerve growth factor support. *Cell Tissue Res*. 1988;254:487-497.

22. Strömberg I, Ebendal T. Aged adrenal medullary tissue survives intraocular grafting, forms nerve fibers, and responds to NGF. *J Neurosci Res*. 1989;23:162-171.

23. Hoehn M, Yahr M. Parkinsonism: onset, progression, and mortality. *Neurology*. 1967;17:427-442.

24. Mobley W, Schenker A, Shooter E. Characterization and isolation of proteolytically modified nerve growth factor. *Biochemistry*. 1976;15:5543-5552.

25. Ebendal T, Olson L, Seiger Å, Belew M. Nerve growth factors in chick and rat tissues. In: Black I, ed. *Cellular and Molecular Biology of Neuronal Development.* New York: Plenum Press; 1984:231-242.

26. Chapman C, Banks B, Carstairs J, Pearce F, Vernon C. The preparation of nerve growth factor from the prostate of the guinea-pig and isolation of immunogenically pure material from the mouse submandibular gland. *Fed Eur Biochem Soc Lett.* 1979;104:341-344.

27. Ebendal T, Olson L, Seiger Å, Hedlund K-O. Nerve growth factors in the rat iris. *Nature.* 1980;286:25-28.

28. Ebendal T. Use of collagen gels to bioassay nerve growth factor activity. In: Rush R, ed. *Nerve Growth Factors.* New York, NY: John Wiley & Sons Inc; 1989:81-93.

29. Lärkfors L, Ebendal T. Highly sensitive enzyme immunoassays for β–nerve growth factor. *J Immunol Methods.* 1987;97:41-47.

30. Hallman H, Farnebo L-O, Hamberger B, Jonsson G. A sensitive method for the determination of plasma catecholamines using liquid chromatography with electrochemical detection. *Life Sci.* 1978;23:1049-1052.

31. Leksell L, Jernberg B. Stereotaxis and tomography: a technical note. *Acta Neurochir (Wien).* 1980;52:1-7.

32. Backlund E. Stereotactic catheter insertion: a new technique. *Neurol Res.* 1987;9:147-150.

33. Hamberger B, Telenius-Berg M, Cedermark B, et al. Subtotal adrenalectomy in multiple endocrine neoplasia type 2. *Henry Ford Hosp Med J.* 1987;35:127-128.

34. Dick M, Guiloff R, Stewart A, et al. Mini-Mental State examination in neurological patients. *J Neurol Neurosurg Psychiatry.* 1984;47:496-499.

35. Deecke L, Englitz H, Kornhuber H, Schmidt G. Cerebral potentials preceding voluntary movements in patients with bilateral or unilateral parkinsonian akinesia. *Prog Clin Neurophysiol.* 1977;1:151-163.

36. Dick J, Cantello R, Buruma O, et al. The bereitschafts-potential, L-dopa and Parkinson's disease. *Electroencephalogr Clin Neurophysiol.* 1987;66:263-274.

37. Freedman R, Adler L, Gerhardt G, et al. Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull.* 1987;13:669-678.

38. Adler L, Waldo M, Freedman R. Neurophysiologic studies of sensory gating in schizophrenia: comparison of auditory and visual responses. *Biol Psychiatry.* 1985;20:1284-1296.

39. Grizzle J, Starmer C, Koch G. Analysis of categorical data by linear models. *Biometrics.* 1969;625:489-504.

40. Seber G, Wild C. *Nonlinear Regression.* New York, NY: John Wiley and Sons Inc; 1989.

41. Angeletti R, Bradshaw R. Nerve growth factor from mouse submaxillary gland: amino acid sequence. *Proc Natl Acad Sci U S A.* 1971;68:2417-2420.

42. Scott J, Selby M, Urdea M, et al. Isolation and nucleotide sequence of a cDNA encoding the precursor of mouse nerve growth factor. *Nature.* 1983;302:538-540.

43. Ullrich A, Gray A, Berman C, Coussens L, Dull TJ. Sequence homology of human and mouse β-NGF subunit genes. *Cold Spring Harb Symp Quant Biol.* 1983;1:435-442.

44. Tischler, DeLellis R, Biales B, et al. Nerve growth factor–induced neurite outgrowth from normal human chromaffin cells. *Lab Invest.* 1980;43:399-409.

45. Korsching S, Thoenen H. Nerve growth factor in sympathetic ganglia and corresponding target organs of the rat: correlation with density of sympathetic innervation. *Proc Natl Acad Sci U S A.* 1983;80:3513-3516.

46. Olson L. Fluorescence histochemical evidence for axonal growth and secretion from transplanted adrenal medullary tissue. *Histochemie.* 1970;22:1-7.

47. Freed WJ, Cannon-Spoor HE, Krauthamer E. Intrastriatal adrenal medulla grafts in rats: long-term survival and behavioral effects. *J Neurosurg.* 1986;65:664-670.

48. Strömberg I, Ebendal T, Seiger Å, Olson L. Nerve fiber production by intraocular adrenal medullary grafts: stimulation by nerve growth factor or sympathetic denervation of the host iris. *Cell Tissue Res.* 1985;241:241-249.

49. Whittemore SR, Ebendal T, Lärkfors L, et al. Developmental and regional expression of β–nerve growth factor messenger RNA and protein in the rat central nervous system. *Proc Natl Acad Sci U S A.* 1986;83:817-821.

50. Korsching S, Auburger G, Heumann R, Scott J, Thoenen H. Levels of nerve growth factor and its mRNA in the central nervous system of the rat correlate with cholinergic innervation. *EMBO J.* 1985;4:1389-1393.

51. Hurtig H, Joyce J, Sladek J Jr, Trojanowski JQ. Postmortem analysis of adrenal-medulla-to-caudate autograft in a patient with Parkinson's disease. *Ann Neurol.* 1989;25:607-614.

52. Landau W. Clinical neuromythology, VII: artificial intelligence: the brain transplant cure for parkinsonism. *Neurology.* 1990:40:733-740.

53. Sladek J Jr, Redmond D Jr, Collier T, et al. Fetal dopamine neural grafts: extended reversal of methylphenyltetrahydropyridine-induced parkinsonism in monkeys. *Prog Brain Res.* 1988;78:497-506.

54. Hansen J, Kordower J, Fiandaca M, et al. Adrenal medullary autografts into the basal ganglia of Cebus monkeys: graft viability and fine structure. *Exp Neurol.* 1988;102:65-75.

55. Goetz C, Tanner C, Penn R, et al. Adrenal medullary transplant to the striatum of patients with advanced Parkinson's disease: 1-year motor and psychomotor data. *Neurology.* 1990;40:273-276.

56. Lieberman A, Ransohoff J, Berczeller P, et al. Adrenal medullary transplants as a treatment for advanced Parkinson's disease. *Acta Neurol Scand Suppl.* 1989;126:189-196.

57. Apuzzo M, Neal J, Water C, et al. Utilization of unilateral and bilateral stereotactically placed adrenomedullary-striatal autografts in parkinsonian humans: rationale, techniques, and observations. *Neurosurgery.* 1990;26:746-757.

58. Allen G, Burns R, Tulipan N, Parker R. Adrenal medullary transplantation to the caudate nucleus in Parkinson's disease: initial clinical results in 18 patients. *Arch Neurol.* 1989;46:487-491.

59. Ahlskog J, Kelly P, van Heerden J, et al. Adrenal medullary transplantation into the brain for treatment of Parkinson's disease: clinical outcome and neurochemical studies. *Mayo Clin Proc.* 1990;65:305-328.

60. Kelly P, Ahlskog J, van Heerden J, et al. Adrenal medullary autograft transplantation into the striatum of patients with Parkinson's disease. *Mayo Clin Proc.* 1989;64:292-290.

61. Bohn MC, Cupit L, Marciano F, Gash DM. Adrenal medulla grafts enhance recovery of striatal dopaminergic fibers. *Science.* 1987;237:913-916.

62. Fiandaca MS, Kordower JH, Hansen JT, Jiao SS, Gash DM. Adrenal medullary autografts into the basal ganglia of Cebus monkeys: injury-induced regeneration. *Exp. Neurol.* 1988;102:76-91.

63. Claude P, Parada IM, Gordon KA, D'Amore PA, Wagner JA. Acidic fibroblast growth factor stimulates adrenal chromaffin cells to proliferate and to extend neurites, but is not a long-term survival factor. *Neuron.* 1988;1:783-790.

64. Stemple DL, Mahanthappa NK, Anderson DJ. Basic FGF induces neuronal differentiation, cell division, and NGF dependence in chromaffin cells: a sequence of events in sympathetic development. *Neuron.* 1988;1:517-525.

65. Leibrock J, Lottspeich F, Hohn A, et al. Molecular cloning and expression of brain-derived neurotrophic factor. *Nature.* 1989;341:149-152.

66. Hohn A, Leibrock J, Bailey K, Barde Y-A. Identification and characterization of a novel member of the nerve growth factor/brain-derived neurotrophic factor family. *Nature.* 1990;344:339-341.

67. Maisonpierre PC, Belluscio L, Squinto S, et al. Neurotrophin-3: a neurotrophic factor related to NGF and BDNF. *Science.* 1990;247:1446-1451.

68. Rosenthal A, Goeddel DV, Nguyen T, et al. Primary structure and biological activity of a novel human neurotrophic factor. *Neuron.* 1990;4:767-773.

69. Ernfors P, Ibanez CF, Ebendal T, Olson L, Persson H. Molecular cloning and neurotrophic activities of a protein with structural similarities to β–nerve growth factor: developmental and topographical expression in the brain. *Proc Natl Acad Sci U S A.* 1990;87:5454-5458.

70. Ayer-LeLievre C, Olson L, Ebendal T, Seiger Å, Persson H. Expression of the β–nerve growth factor gene in hippocampal neurons. *Science.* 1988;240:1339-1341.

71. Wetmore C, Ernfors P, Persson H, Olson L. Localization of brain-derived neurotrophic factor mRNA to neurons in the brain by in situ hybridization. *Exp Neurol.* 1990;109:141-152.

72. Ernfors P, Lindefors N, Chan-Palay V, Persson H. Cholinergic neurons of nucleus basalis express elevated levels of nerve growth factor receptor mRNA in senile dementia of the Alzheimer type. *Dementia.* In press.

73. Goedert M A, Dawbarn D, Whilcock C, Chao M. Nerve growth factor receptor mRNA distribution in human brain: normal levels in basal forebrain in Alzheimer's disease. *Brain Res Mol Brain Res.* 1989;5:1-7.

74. Ebendal T. NGF in CNS: experimental data and clinical implications. *Prog Growth Factor Res.* 1989;1:143-159.

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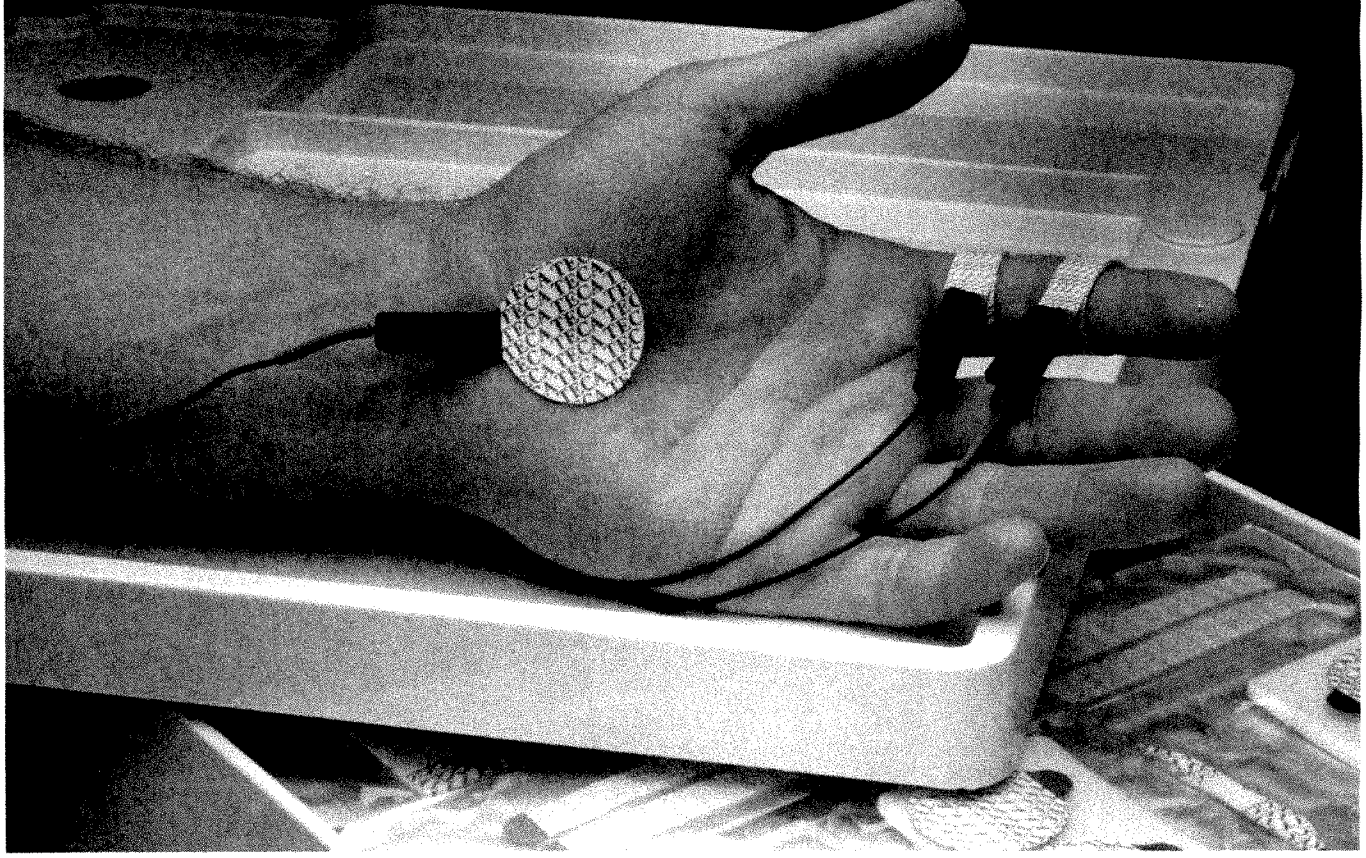

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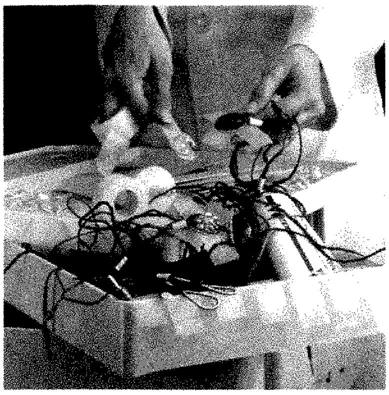

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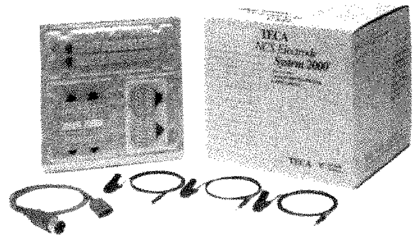

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Prednisone in Duchenne Dystrophy

A Randomized, Controlled Trial Defining the Time Course and Dose Response

Robert C. Griggs, MD; Richard T. Moxley III, MD; Jerry R. Mendell, MD;
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J. Philip Miller; and the Clinical Investigation of Duchenne Dystrophy Group

• A randomized, controlled trial of daily prednisone was conducted in 99 boys (aged 5 to 15 years) with Duchenne dystrophy to define the time course of improvement and the dose response to treatment. Prednisone at 0.3 mg/kg (n = 33), prednisone at 0.75 mg/kg (n = 34), and placebo (n = 32) were administered for 6 months. Patients were examined using manual muscle and myometry testing, timed functional testing, pulmonary function testing, and laboratory measurements at 10 days, 1 month, 2 months, 3 months, and 6 months of treatment. Boys treated with prednisone had stronger average muscle strength scores, than did boys treated with placebo as early as 10 days after starting therapy. At the 3-month visit, the boys in the group given 0.75 mg/kg of prednisone were significantly stronger than those in the group given 0.3 mg/kg of prednisone, indicating a dose response. At 6 months, significant side effects occurred in the group treated with 0.75 mg/kg of prednisone, including weight gain, cushingoid appearance, and excessive hair growth. Only weight gain was observed in the group taking prednisone at a dose of 0.3 mg/kg. Importantly, no side effects were evident at 10 days or 1 month of treatment, despite improvement in muscle strength and function. We conclude that prednisone produces a rapid increase in muscle strength in patients with Duchenne dystrophy and that this improvement is maximal at a prednisone dosage of 0.75 mg/kg or less.

(*Arch Neurol.* 1991;48:383-388)

Duchenne muscular dystrophy is an X-linked recessive disorder that results from a gene defect causing a deficiency of the cytoskeletal protein, dystrophin.[1] The potential replacement of dystrophin by transfer of normal myoblasts is under study,[2-4] and the possibility of direct gene replacement has also been considered.[5] However, only one form of treatment has been shown to alter the course of the disease. In a recent double-blind, randomized, controlled trial, prednisone treatment in the dosage of 0.75 mg/kg per day or 1.5 mg/kg per day resulted in a significant improvement in strength and function of patients with Duchenne dystrophy,[6] confirming our own[7] and other previous observations.[8] The present study was designed to obtain additional data on the effectiveness of prednisone in Duchenne dystrophy; determine the dose response for prednisone by comparing a dosage of 0.75 mg/kg with a smaller one, 0.3 mg/kg; determine the time course of improvement by performing earlier tests of strength; and provide additional data on side effects of prednisone.

PATIENTS AND METHODS

Patients

A total of 99 patients, 5 to 15 years old, with Duchenne dystrophy, as defined in previous investigations,[9-11] were studied at the five collaborating institutions (University of Alberta, Edmonton; University of Rochester (NY); The Ohio State University, Columbus; Washington University, St Louis, Mo; and Vanderbilt University, Nashville, Tenn). The Institutional Review Board at each center approved the protocol. After informed consent was obtained from the parents in the presence of an auditor witness, patients were randomized to one of three treatment groups: placebo (n = 32), 0.3 mg/kg of prednisone (n = 33), and 0.75 mg/kg of prednisone (n = 34). Prednisone dose was rounded off to the nearest 5 mg. The study was a 6-month, double-blind trial.

Medication

Gelatin capsules (No. 3 Eli Lily, Indianapolis, Ind) containing powdered prednisone (Spectrum, Gardena, Calif) or placebo were prepared and dispensed from the pharmacy at the University of Rochester (NY), Strong Memorial Hospital. Placebo was administered as a capsule that weighed 240 mg and contained powdered lactose. Prednisone was prepared in a capsule containing the appropriate dose and sufficient lactose to give a capsule that weighed 240 mg. After the initial evaluation, each patient was provided with a 6-month supply of medication. A family member dispensed one capsule per day to the patient at breakfast. Compliance was evaluated by weighing the bottle of medication initially and at each return visit.

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Table 1.—Clinical and Laboratory Measurements in the Study Groups Before Treatment

	Mean ± SD* (No. of Patients Completing Testing)			
		Prednisone		
Measurement	**Placebo**	**0.3 mg/kg**	**0.75 mg/kg**	***P* Value†**
Age, y	9.55 ± 2.44 (32)	9.63 ± 2.53 (33)	9.36 ± 2.86 (34)	.91
Muscle strength score	5.80 ± 1.10 (32)	5.78 ± 1.28 (33)	5.63 ± 1.32 (34)	.83
Leg function score	4.16 ± 3.40 (32)	4.29 ± 3.32 (33)	4.26 ± 3.39 (34)	.99
Contracture index	−2.22 ± 0.80 (32)	−2.27 ± 0.92 (33)	−2.07 ± 0.93 (34)	.62
Timed function‡				
Time to climb stairs, s	7.40 ± 4.89 (20)	6.42 ± 4.63 (19)	10.02 ± 9.98 (21)	.42
Time to travel 9 m, s	8.09 ± 4.36 (22)	19.68 ± 30.77 (25)	9.52 ± 12.64 (23)	.21
Time to stand, s	9.43 ± 5.92 (15)	8.56 ± 5.52 (18)	10.59 ± 10.05 (16)	.89
Lifting weights, kg	1.03 ± 0.72 (23)	1.42 ± 0.84 (22)	1.30 ± 0.62 (22)	.20
Pulmonary function				
Forced vital capacity, L	1.51 ± 0.62 (32)	1.54 ± 0.53 (31)	1.35 ± 0.46 (34)	.34
Maximal expiratory pressure, mm Hg	13.23 ± 5.58 (24)	14.13 ± 6.40 (24)	12.28 ± 4.76 (27)	.50
Maximal voluntary ventilation, L	42.56 ± 22.42 (32)	41.52 ± 15.20 (31)	38.59 ± 15.58 (34)	.65
Log$_e$ creatine kinase	8.54 ± 0.70 (20)	8.16 ± 1.01 (23)	8.52 ± 1.05 (22)	.32

*All values represent the mean ± standard deviation of the average of first two evaluations in patients who were able to complete the test.

†By one-way analysis of variance.

‡Means and standard deviations from untransformed data. *P* values from analysis of data after performing a natural-logarithm transformation.

Study Protocol

Patients were admitted to the Clinical Research Center before the start of treatment. During the initial admission to the Clinical Research Center, clinical evaluations were made on 2 consecutive days, after which prednisone was started. Patients were reassessed as outpatients at 10 days, 1 month, 2 months, 3 months, and 6 months. Each outpatient visit included independent clinical and side-effect evaluations obtained by the clinical evaluator and principal investigator, respectively.

Clinical Evaluation

Clinical evaluators tested patients' muscle strength by manual muscle testing of 34 muscle groups, graded according to an expanded 10-point scale, based on the Medical Research Council methods.[12] A score for average muscle strength was derived from these measurements.[11] Muscle strength was also evaluated with a Penney and Giles hand-held myometer,[13] testing the strength at the shoulder abductors, elbow flexors and extensors, and the hip abductors on the right side. The average at the make and break readings (the maximum strength exerted before giving way) was used for analysis. Muscle function was evaluated by timed functional testing, including measurement of the time needed to rise to a standing position from a lying position on the floor, to climb four standard-size steps, and to travel 30 feet (9 m) as rapidly as possible. An overall functional grade was assigned for both the upper and lower extremities. The maximum hand-held weight that could be lifted with the patient sitting was assessed. Pulmonary function tests included measurements of forced vital capacity, maximum voluntary ventilation, and maximal expiratory pressure. All measures except the myometer strength testing were performed as in our previous studies.[9,11]

Laboratory Evaluation

Blood specimens for creatine kinase evaluation were obtained at baseline and after 6 months of treatment, and measurements were performed in a central laboratory.[6]

Blood tests for safety monitoring were performed before prednisone administration and at 6 months, including a complete blood cell count and measurement of serum sodium, potassium, chloride, calcium, phosphate, glucose, carbon dioxide, serum urea, nitrogen, creatinine, bilirubin, alkaline phosphatase, alanine aminotransferase, and aspartate aminotransferase levels.

Side Effects

Patients were examined and parents were interviewed for side effects at both visits prior to initiating treatment and at 1, 2, 3, and 6 months of treatment. These evaluations were performed by the principal investigator physician and did not take place in the presence of clinical evaluators testing patients and recording data. The evaluation included assessment for cataracts, edema, cosmetic, behavioral, and other potential side effects of prednisone therapy. Urinary dipstick for glucose was obtained at each visit. Height, weight, pulse, blood pressure, and temperature were obtained at the same frequency by the Clinical Research Centers' nursing staff. Blood studies were obtained as described above. In addition, the occurrence of all intercurrent events, including infections, coincidental illness and medications, surgery, or other events, were monitored at each visit.

Prior to treatment and at each follow-up visit, patients were instructed to follow a diet low in sodium and simple sugars. Vigorous counseling by the Clinical Research Centers' dieticians was provided to both patients and parents of boys gaining weight. All patients were instructed to take 0.3 g of calcium carbonate with each meal.

Statistical Analysis

At the initial visit to the Clinical Research Center, baseline values were obtained by computing the mean for each variable in each patient. At initial visits, statistical comparisons between the treatment groups were evaluated with use of one-way analysis of variance, and, at subsequent visits, with use of analysis of covariance, in which the value for a treatment group served as the classification variable and the corresponding baseline value for that measure as a covariate. On the basis of our previous experience with the natural history of Duchenne dystrophy, we used natural-logarithm transformations of certain values, when necessary, to control for heteroscedasticity. Average muscle strength was chosen a priori as the primary measure of treatment efficacy. The primary test of each measure was a determination of the differences between the least-square mean for the placebo group and the mean for the two prednisone groups at each visit. Auxiliary assessments included tests of the differences between the placebo group and each prednisone group and the differences between the two prednisone groups. Least-square means (which adjust the treatment-group means for differences in baseline values) were computed for all measures. The *P* values reported for all tests of significance are two sided. Computations were performed with SAS GLM type III sums of squares.[14] The variables were evaluated individually, with no correction for multiple comparisons. Such correction would not materially affect the conclusions, since the uncorrected *P* values were very small. Sample size in this study was sufficient to achieve a power of 0.7 to detect arrest of disease progression within 6 months.

The analysis of the significance of differences in the prevalence of side effects was assessed by a categorical model fit with Proc CATMOD.[14] In the analysis of weight change, a cumulative logit was used as the dependent

Table 2.—Average Muscle Strength (AMS) at Each Visit

	Mean* AMS (No. of Subjects)			P Values			
		Prednisone		Placebo vs Prednisone			
Time	**Placebo**	**0.3 mg/kg**	**0.75 mg/kg**	**0.3 and 0.75 mg/kg**	**0.3 mg/kg**	**0.75 mg/kg**	**Prednisone, 0.3 mg/kg vs 0.75 mg/kg**
10 d	5.78 (31)	5.87 (31)	5.88 (33)	.05	.11	.08	.89
1 mo	5.83 (30)	5.93 (32)	6.01 (34)	.06	.24	.04	.34
2 mo	5.71 (30)	5.89 (32)	6.00 (34)	.0002	.01	.0001	.12
3 mo	5.68 (29)	5.86 (32)	6.02 (34)	.0001	.02	.0001	.02
6 mo	5.48 (30)	5.82 (31)	6.00 (34)	.0001	.0001	.0001	.03

*Least-square means (adjusted for baseline values).

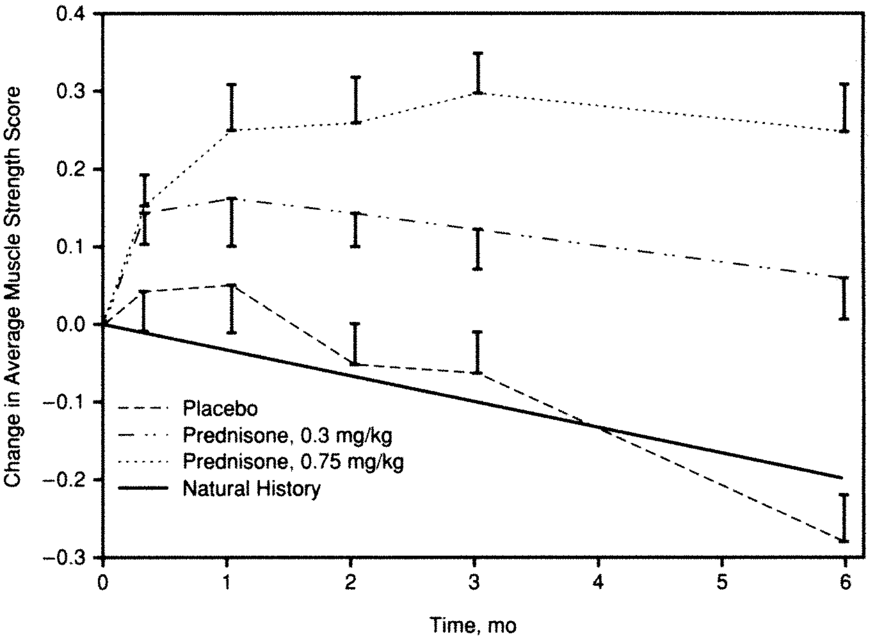

Fig 1.—Change (mean ± SEM) in the score for average muscle strength in the placebo and prednisone groups after the initiation of their regimens. Solid line ("natural history") represents the values for change observed in 177 patients with Duchenne dystrophy who received no treatment.

variable. For other side effects, the default logit response was employed. Contrasts were computed as for the measures of efficacy. The power of this study to detect differences in side effects between groups is inadequate except for major changes.

RESULTS

Baseline Assessments

There were no significant differences between the three patient groups in any baseline values for age, muscle strength score, leg function grade, timed functional testing, ability to lift weights, pulmonary function, or creatine kinase concentration (Table 1). (For certain patients, disability precluded testing of a specific function.)

Results of Treatment

At 10 days, the average muscle strength of the low-dose (5.87) and high-dose (5.88) groups was significantly greater ($P = .05$) than that for the placebo-treated group (5.78) (Table 2). This improvement increased at 1 month and then reached a plateau that persisted until 6 months (Fig 1 and Table 2) and contrasted with the placebo group that became steadily weaker. The increase in average muscle strength above baseline at 6 months was similar to that observed at 3 months for both patient groups. The higher dose of prednisone (0.75 mg/kg) produced a greater increase in muscle strength at each time point than did the low dose (0.3 mg/kg), although the difference did not become statistically significant until 3 months ($P = .02$) (Fig 1). The placebo group declined in muscle strength similarly to the natural history rate of decline previously observed in Duchenne dystrophy.[7,9]

At 6 months, the high-dose and low-dose prednisone groups were significantly improved compared with placebo group in leg function grade, timed functions, lifting weights, and forced vital capacity. The improvement was statistically greater in the high-dose prednisone group for most measures (Table 3). In the low-dose prednisone group, some measures did not change when compared with placebo (Table 3).

Side Effects

The incidence of side effects in the three study groups is indicated in Table 4. Patients taking prednisone at 0.75 mg/kg per day had a significant incidence of cushingoid appearance (71%), excessive hair growth (41%), and increased appetite (68%). Patients taking 0.3 mg/kg of prednisone per day did not have any side effects that were present to a significantly greater extent than those reported in the placebo group. There was a trend for patients taking 0.3 mg/kg of prednisone daily to have an increased appetite ($P = .10$).

Significant weight gain occurred in both prednisone-treated groups (Table 5; Fig 2), and, although a smaller percentage of patients gained over 20% above baseline on the 0.3-mg/kg dosage, the difference was not significant between groups (0.3 mg of prednisone, 11%; 0.75 mg of prednisone, 31%; $P = .18$). Neither group of patients gained significantly more than placebo-treated patients until 2 months of treatment (Fig 2).

COMMENT

This study confirms our previous, controlled, double-blind, therapeutic trial showing that prednisone produces a significant *increase* in muscle strength, pulmonary function, and functional ability in patients with Duchenne dystrophy. In addition, the present study helps to define the minimum prednisone dose required to produce the maximal increase in strength to be between 0.3

Table 3.—Clinical and Laboratory Measurements in the Study Groups After 6 Months of Treatment

	Mean* (No. of Patients Completing Testing)			P Value			
		Prednisone		Placebo vs Prednisone			
Measurement	Placebo	0.3 mg/kg	0.75 mg/kg	0.3 and 0.75 mg/kg	0.3 mg/kg	0.75 mg/kg	Prednisone, 0.3 mg/kg vs 0.75 mg/kg
Muscle strength score	5.48 (30)	5.82 (31)	6.00 (34)	.0001	.0001	.0001	.026
Leg function grade	4.46 (29)	4.07 (29)	4.19 (34)	.064	.060	.17	.53
Timed function†							
Time to climb stairs, s	8.44 (17)	5.76 (17)	4.23 (20)	.0001	.0001	.0001	.0014
Time to travel 9 m, s	8.51 (19)	7.33 (21)	6.37 (23)	.01	.12	.003	.127
Time to stand, s	8.23 (17)	6.64 (17)	4.56 (16)	.005	.15	.0003	.004
Lifting weights, kg	1.26 (18)	1.64 (21)	2.04 (22)	.0001	.003	.0001	.0006
Pulmonary function							
Forced vital capacity, L	1.48 (30)	1.64 (29)	1.67 (34)	.0006	.006	.001	.67
Maximal expiratory pressure, mm Hg	14.64 (21)	15.00 (22)	16.76 (27)	.20	.75	.055	.10
Maximal voluntary ventilation, L	44.17 (30)	46.90 (29)	46.06 (34)	.28	.28	.44	.73
Log$_e$ creatine kinase	9.26 (9)	9.21 (9)	9.15 (8)	.73	.85	.69	.83

*Values represent the least-square means (adjusted for corresponding baseline).
†Mean values are in original units from log transformations.

Table 4.—Side Effects in Study Groups*

	No. (%) With Side Effect			P Values			
		Prednisone		Placebo vs Prednisone			
Side Effect	Placebo (n = 32)	0.3 mg/kg (n = 33)	0.75 mg/kg (n = 34)	0.3 and 0.75 mg/kg	0.3 mg/kg	0.75 mg/kg	Prednisone, 0.3 mg/kg vs 0.75 mg/kg
Ankle edema	0 (0)	1 (3)	2 (6)	.51	.69	.40	.60
Acne	4 (13)	3 (9)	9 (26)	.68	.66	.18	.08
Insomnia	2 (6)	3 (9)	6 (18)	.35	.67	.19	.33
Anorexia	4 (13)	1 (3)	1 (3)	.08	.18	.17	.97
Cushingoid	11 (35)	13 (41)	24 (71)	.06	.67	.006	.02
Hair growth	4 (13)	3 (9)	14 (41)	.35	.66	.02	.006
Hyperactivity	4 (13)	5 (16)	8 (26)	.44	.76	.28	.42
Irritability	12 (39)	11 (34)	17 (50)	.76	.72	.36	.20
Increased appetite	12 (39)	19 (59)	23 (68)	.02	.10	.02	.49
Glycosuria	0	0	1 (3)	.87	.97	.73	.71
Cataracts	0	0	0	...	...	...	...

*Includes all side effects reported at visits 1, 2, 3, and 6 months.

Table 5.—Weight Gain in the Study Groups*

	No. of Patients (% of Group With Weight Gain)		
		Prednisone	
Percent of Weight Gained Above Baseline	Placebo	0.3 mg/kg	0.75 mg/kg
<5	16 (55)	6 (22)	3 (9)
5-10	6 (21)	8 (30)	5 (16)
11-20	6 (21)	10 (37)	14 (44)
>20	1 (3)	3 (11)	10 (31)

*Weight at the first visit was compared with weight at the last visit. The weight gain in the prednisone-treated patients was significant (placebo vs both prednisone groups, $P = .0002$; placebo vs prednisone 0.3 mg/kg, $P = .01$; placebo vs prednisone 0.75 mg/kg $P = .0005$). There was no significant difference in weight gain between the prednisone groups ($P = .18$).

and 0.75 mg/kg. The improvement is rapid and demonstrable within 10 days of starting the drug, becoming maximal by 2 months of treatment.

This study design has a major advantage over the previously reported randomized, double-blind, controlled trial, since the improvement in strength at 10 days occurred prior to the onset of demonstrable side effects, excluding observable differences between treatment and placebo groups as a potentially unblinding factor. Side effects remained absent at the 1-month evaluation. Furthermore, as in the previous double-blind study,[6] there were independent roles for clinical evaluators involved in assessment of strength and function, and principal investigators, who assessed side effects.

We have considered the mechanism of prednisone-induced improvement in our patients. The possibility that the response is a placebo effect is discounted by the use of a randomized, double-blind, placebo-controlled trial in both the present and previous[6] studies. In addition, the response observed represented a rapid and sustained improvement when compared with the natural history, which we have charted in over 200 patients with Duchenne dystrophy.[7,9] Moreover, four negative double-blind, randomized, controlled trials of other medications have provided us with ample data on placebo effects in Duchenne dystrophy.[15-18]

The possibility that prednisone pro-

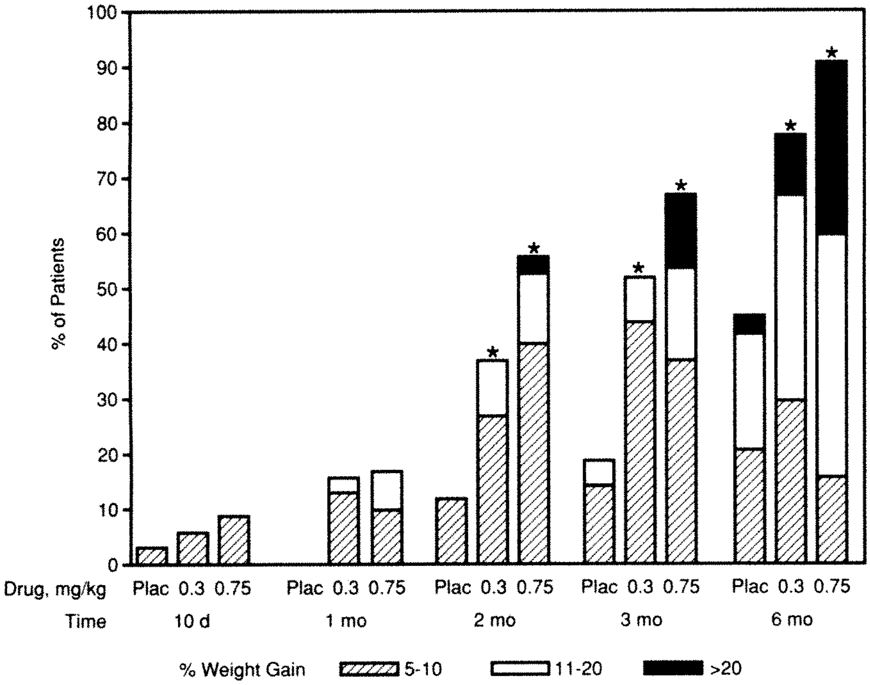

Fig 2.—Percent weight gain of patients with Duchenne dystrophy treated with placebo (Plac) and prednisone, 0.3 mg/kg per day or 0.75 mg/kg per day, at each visit. Values significantly ($P<.05$) different from those in the placebo group are indicated with an asterisk.

duced its benefit by a psychological effect in terms of an increase in motivation was considered. However, the observation of an increase in muscle mass as demonstrated by creatinine excretion in our previous trial[6] provided confirmatory evidence of an actual change in the pathological process within muscle in treated patients. In companion studies conducted in conjunction with our initial treatment trials for prednisone in Duchenne dystrophy, we showed that total body potassium increased to an extent similar to creatinine excretion.[7] Total body potassium provides an independent assessment of lean body mass[19] and confirmed that the increase in creatinine excretion reflects an increase in muscle mass.

Additional studies conducted concurrently with our earlier randomized trial of prednisone[6] have begun to define the basis for the increase in muscle mass, which accompanies the improvement in strength. Measurements of 24-hour urinary excretion of 3-methylhistidine were made before and after 6 months in 103 patients with Duchenne dystrophy.[20] The rate of 3-methylhistidine excretion was adjusted for muscle mass. Six months of prednisone treatment produced a significant decline in 3-methylhistidine excretion (16%), compared with the 3% increase observed in untreated patients.[20] Since 3-methylhistidine is an indirect measure of the rate of muscle breakdown,[21] it appears that muscle mass increases, at least in part, because of a decrease in the rate of muscle breakdown.

Studies carried out at one of the five centers (The Ohio State University) in a subgroup of patients with Duchenne dystrophy addressed the question of the immunosuppressant actions of prednisone in mediation of improved strength and decreased in muscle destruction. Mononuclear cell analyses of muscle biopsy specimens conducted at the conclusion of the prednisone trial demonstrated a marked decrease in the total number of T cells (CD2+) and selectively on the subset of CD8+ cytotoxic/suppressor T cells.[22] Prednisone treatment did not alter the number of necrotic fibers or decrease the infiltration of CD4+, natural killer cells, or macrophages, or the number of B cells.[22] Prednisone treatment had no effect on dystrophin expression following treatment.[23] Thus, it appears that prednisone produces an increase in strength and muscle mass by decreasing the rate of muscle breakdown. However, since the number of necrotic fibers is not decreased, it is possible that the prednisone-induced decrease in cytotoxic lymphocytes allows damaged fibers to undergo regeneration averting muscle breakdown and fiber loss, as reflected by the decrease in 3-methylhistidine excretion. Studies by others in Duchenne dystrophy have shown that the complement cascade is activated in necrotic fibers[24] and that cytotoxic T cells focally invade muscle fibers.[25]

The observations that prednisone improves strength and function in Duchenne dystrophy in this and previous studies,[7,8] as well as reducing inflammatory infiltrates, decreasing 3-methylhistidine urinary excretion, and increasing muscle mass, are not inconsequential in a disease of relentless progression without treatment. Although clinical trials of myoblast transfer in boys with Duchenne dystrophy[26] have begun in hopes of producing dystrophin expression as seen in the mdx mouse model for the disease,[2,3] the widespread applicability of such treatment is unknown.[4] For this reason, we believe that additional studies of the mechanism of prednisone effect on rates of muscle protein synthesis and regulation of hormonal milieu are important. We are also examining the effect of azathioprine in combination with prednisone for a potential steroid-sparing or potentiating effect.[27] Controlled studies of patients with more advanced Duchenne dystrophy and with Becker's dystrophy are in progress. It is also possible that other schedules of prednisone administration (such as pulsed dosage) may be effective and have fewer side effects.

For the present, our studies have defined a dose response to prednisone with maximal benefit achieved at 0.75 mg/kg per day, not equaled by 0.3 mg/kg per day. We recommend that a prednisone dosage of 0.75 mg/kg per day be considered for patients with Duchenne dystrophy who experience functional decline. Our natural history data suggest that patients are most likely to begin such functional decline at age 7.5 years[28] (falling more frequently, more trouble with stair climbing), requiring use of long leg braces between 9 and 10 years. Studies in progress also indicate that long-term prednisone continues to maintain strength and function compared with natural history rates of decline.[29] Side effects such as weight gain, hypertension, or behavioral disturbances may necessitate the reduction or cessation of treatment in some patients.[6,29]

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References

1. Koenig M, Monaco, AP, Kunkel LM. The complete sequence of dystrophin predicts a rod-shaped cytoskeletal protein. *Cell.* 1988;53:219-228.
2. Partridge TA, Morgan JE, Coulton GR, Hoffman EP, Kunkel LM. Conversion of mdx myofibres from dystrophin-negative to -positive by injection of normal myoblasts. *Nature.* 1989;337:176-179.
3. Karpati G, Pouliot Y, Zubrzycka-Gaarn EE, et al. Dystrophin is expressed in mdx skeletal muscle fibres after normal myoblast implantation. *Am J Pathol.* 1989;134:27-32.
4. Griggs RC, Karpati G (eds). *Myoblast Transfer.* New York, NY: Plenum Press; 1990.
5. Wolfe JA, Malone RW, Williams P. Direct gene transfer into mouse muscle in vivo. *Science.* 1990;23:1465-1468.
6. Mendell JR, Moxley RT III, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. *N Engl J Med.* 1989;320:1592-1597.
7. Brooke MH, Fenichel GM, Griggs RC, et al. Clinical investigation of Duchenne muscular dystrophy: interesting results in a trial of prednisone. *Arch Neurol.* 1987;44:812-817.
8. Drachman DB, Toyka RV, Myer E. Prednisone in Duchenne muscular dystrophy. *Lancet.* 1974;2:1409-1412.
9. Brooke MH, Fenichel GM, Griggs RC, et al. Clinical investigation in Duchenne dystrophy, II: determination of the 'power' of therapeutic trials based on the natural history. *Muscle Nerve.* 1983;6:91-103.
10. Mendell, JR, Province MA, Moxley RT III, et al. Clinical investigation of Duchenne muscular dystrophy: a methodology for therapeutic trials based on natural history controls. *Arch Neurol.* 1987;44:808-811.
11. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy, I: the design of the protocol. *Muscle Nerve.* 1981;4:186-197.
12. Medical Research Council. *Aids to the Investigation of Peripheral Nerve Injuries.* London, England: Her Majesty's Stationery Office; 1976.
13. Edwards RHT, McDonnell M. A handheld clinical dynamometer for evaluating voluntary muscle function in patients. *Lancet.* 1974;2:757-758.
14. SAS Institute Inc. *SAS User's Guide: Statistics, Version 6.03 Edition.* Cary, NC: SAS Institute Inc: 1988:549-640.
15. Mendell JR, Griggs RC, Moxley RT III, et al. Clinical investigation in Duchenne muscular dystrophy, IV: double-blind controlled trial of leucine. *Muscle Nerve.* 1984;7:535-541.
16. Moxley RT III, Brooke MH, Fenichel GM, et al. Clinical investigation in Duchenne dystrophy, VI: double-blind controlled trial of nifedipine. *Muscle Nerve.* 1987;10:22-23.
17. Fenichel GM, Brooke MH, Griggs RC, et al. Clinical investigation in Duchenne muscular dystrophy: double-blind controlled trial of penicillamine and vitamin E. *Muscle Nerve.* 1988;11:1164-1168.
18. Griggs RC, Moxley RT III, Mendell JR, et al. Randomized, double-blind trial of mazindol in Duchenne dystrophy. *Muscle Nerve.* 1990;13:1169-1173.
19. Griggs RC, Forbes G, Moxley RT III, Herr BE. The assessment of muscle mass in progressive neuromuscular disease. *Neurology.* 1983;33:158-165.
20. Moxley RT III, Lorenson M, Griggs RC, et al. Decreased breakdown of muscle protein after prednisone therapy in Duchenne dystrophy (DD). *J Neurol Sci.* 1990;98(suppl):419.
21. Griggs RC, Rennie MJ. Muscle wasting in muscular dystrophy: decreased protein synthesis or increased degradation? *Ann Neurol.* 1983;13:125-132.
22. Kissel JT, Burrow K, Rammohan KW, Mendell JR, and CIDD Group. Mononuclear cell analysis of muscle biopsies in prednisone-treatment Duchenne muscular dystrophy. *Neurology.* 1990;40:412.
23. Burrow KL, Coovert D, Klein CJ, et al. Dystrophin analysis following prednisone treatment of Duchenne muscular dystrophy. *Neurology.* 1990;40:206.
24. Engel AG, Beisecker G. Complement activation in muscle fiber necrosis: demonstration of the membrane attack complex of complement in necrotic fibers. *Ann Neurol.* 1982;12:289-296.
25. Arahata K, Engel AG. Monoclonal antibody analysis of mononuclear cells in myopathies, I: quantitation of subsets according to diagnosis and sites of accumulation and demonstration and counts of muscle fibers invaded by T-cells. *Ann Neurol.* 1984;16:193-208.
26. Law PK, Fang Q, Goodwin TG, et al. First clinical trial of myoblast transfer therapy. *J Neurol Sci.* 1990;98(suppl):32.
27. Steinberg AD, Plotz PH, Wolff SM, et al. Cytotoxic drugs in the treatment of nonmalignant diseases. *Ann Intern Med.* 1972;76:619-642.
28. Brooke MH, Fenichel GM, Griggs RC, et al. Duchenne muscular dystrophy: patterns of clinical progression and effects of supportive therapy. *Neurology.* 1989;39:475-481.
29. Fenichel GM, Mendell JR, Moxley RT III, et al. A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. *Arch Neurol.* In press.

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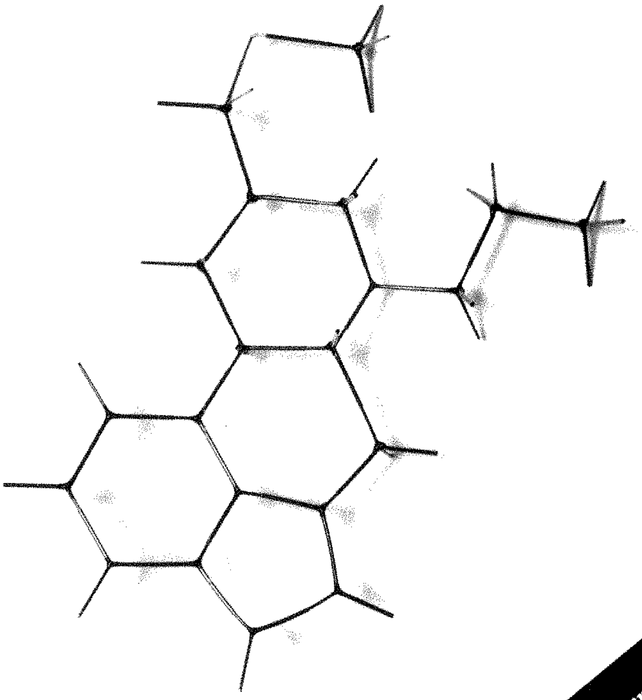

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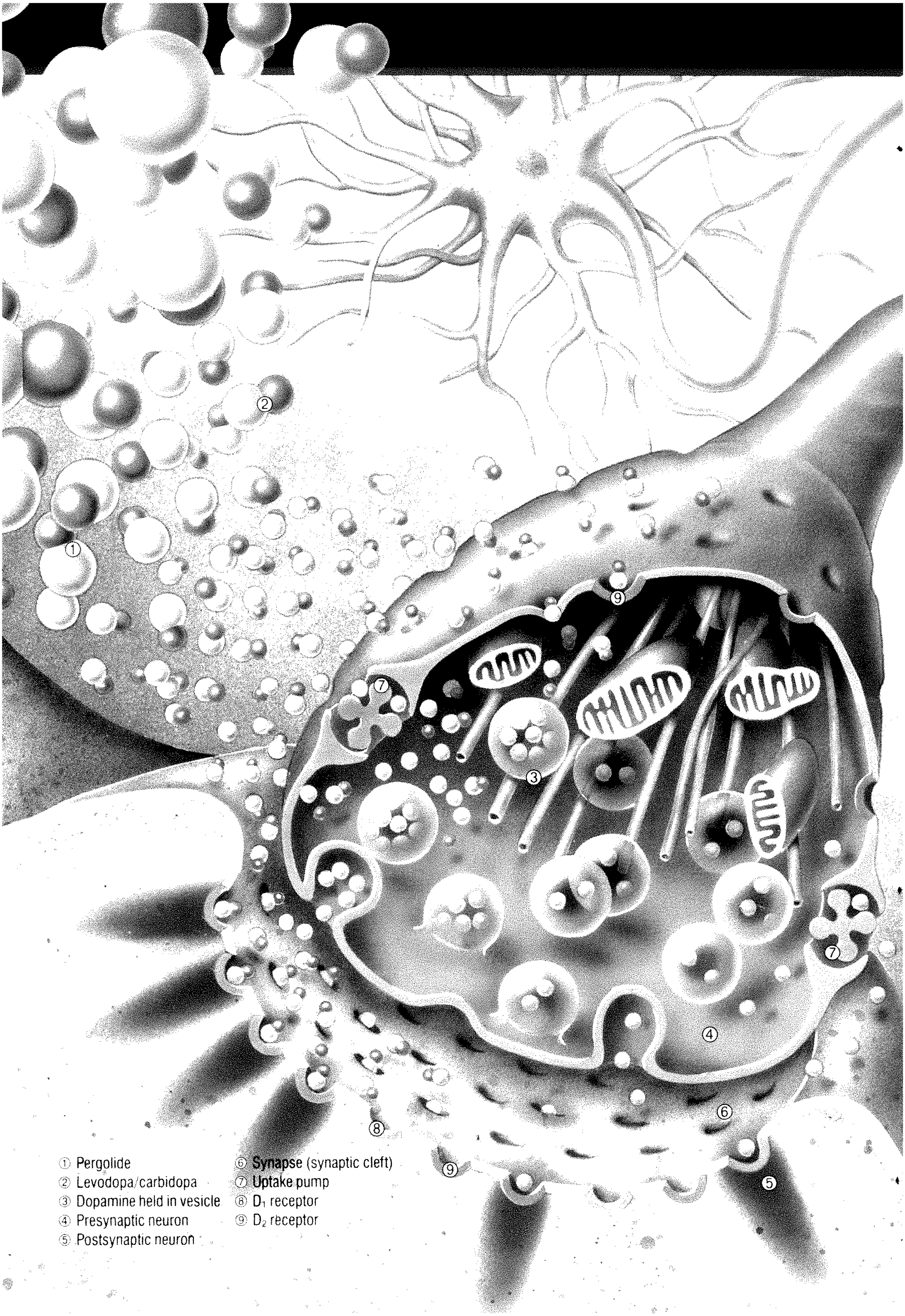
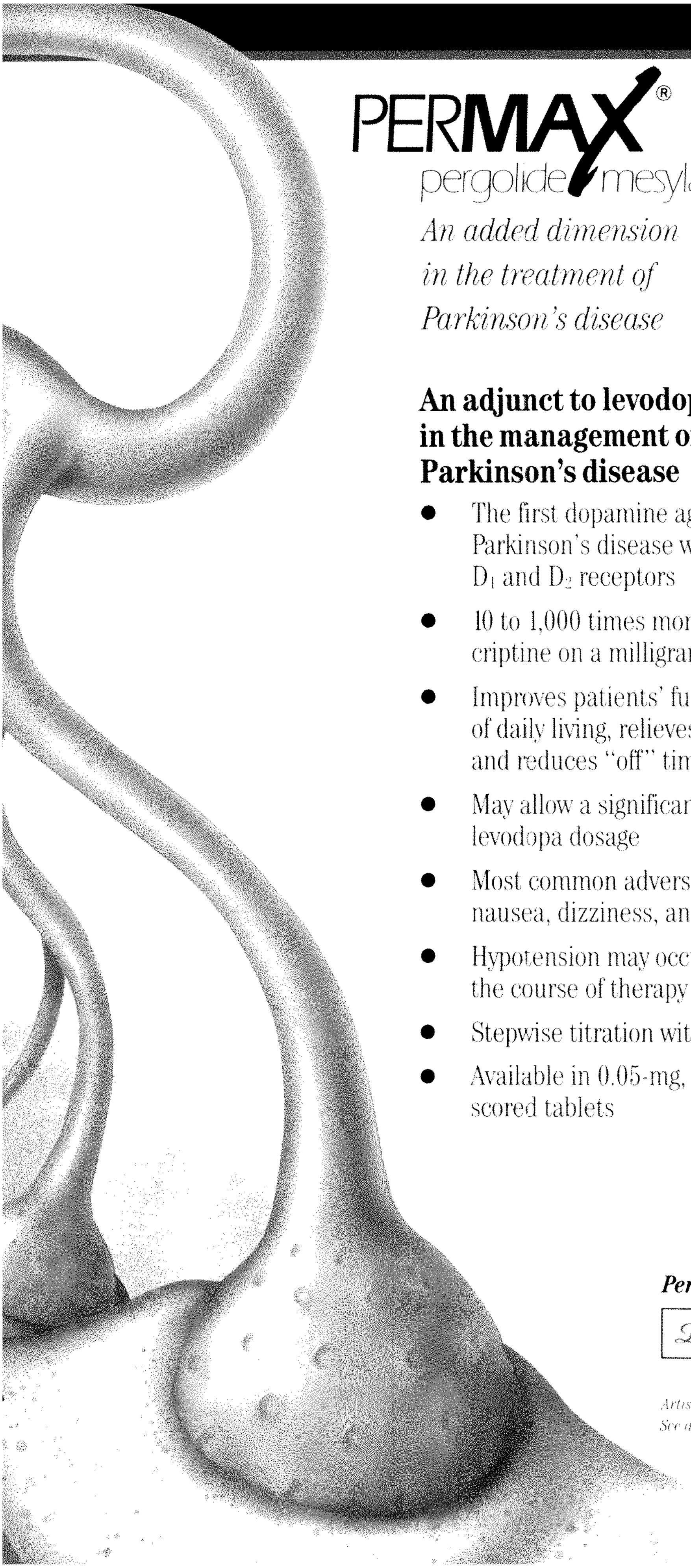


① Pergolide
② Levodopa/carbidopa
③ Dopamine held in vesicle
④ Presynaptic neuron
⑤ Postsynaptic neuron
⑥ **Synapse** (synaptic cleft)
⑦ **Uptake** pump
⑧ D_1 receptor
⑨ D_2 receptor



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Permax*

pergolide mesylate

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to levodopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the sample of patients evaluated had been on levodopa/carbidopa for 3.9 years (range, two days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of levodopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

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There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia, and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities —*See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Body System/ Adverse Event*	Percentage of Patients Reporting Events Pergolide Mesylate N=189	Placebo N=187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax —This section reports event frequencies evaluated as of October 1988 for adverse events ocurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System —*Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System —*Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusion, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System —*Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

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Positron Emission Tomography in Progressive Supranuclear Palsy

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• Positron emission tomography with 6-[^{18}F]fluoro-L-dopa (6-FD) provides in vivo information on the function of nigrostriatal dopaminergic neurons. We used 6-FD and positron emission tomography to investigate the integrity of the nigrostriatal system in seven patients with progressive supranuclear palsy. All patients had axial hypertonia, vertical gaze palsy, and parkinsonian features. Dementia, pyramidal signs, and ataxia were seen in varying proportions. We analyzed the scans with a graphic method to calculate a steady-state 6-FD uptake rate constant for the whole striatum. Results were compared with those obtained in seven age-matched controls. As a group, the patients with progressive supranuclear palsy had reduced 6-FD uptake constants. The 6-FD uptake constant correlated inversely with the duration of the disease. Normal positron emission tographic findings in one patient with the shortest duration of symptoms suggests that in early progressive supranuclear palsy, parkinsonism may relate to dysfunction distal to the dopaminergic neurons.

(*Arch Neurol.* 1991;48:389-391)

Progressive supranuclear palsy (PSP) is characterized by supranuclear ophthalmoplegia, parkinsonism, pseudobulbar palsy, axial hypertonia, and dementia with variable cerebellar ataxia and pyramidal dysfunction.[1-3] The parkinsonism in PSP may be related, at least in part, to dysfunction of the dopaminergic pathway. In vivo studies with positron emission tomography (PET) should add to our understanding of the pathophysiologic processes involved in disorders in which the dopaminergic pathways may be preferentially affected, such as PSP. Positron emission tomography is particularly suited for the evaluation of early disease, in which postmortem information is seldom available.

With 6-[^{18}F]fluoro-L-dopa (6-FD) and PET, we can study the integrity of nigrostriatal dopaminergic function. The injected 6-FD is transferred from blood to the striatum, where it is converted to fluorodopamine by dopa-decarboxylase and trapped in the presynaptic vesicles. The retention of radioactivity within the striatum is related to the functional integrity of the presynaptic nigrostriatal dopaminergic nerve endings. This can be quantified by calculating a 6-FD uptake rate constant.[4] In idiopathic parkinsonism, the accumulation of 6-FD and its metabolites in the striatum is decreased, implying impairment in the presynaptic nigrostriatal dopaminergic function.[5-7]

The aim of this study was to utilize PET to evaluate presynaptic nigrostriatal dopaminergic function in PSP.

The diagnosis of PSP was independently confirmed by two neurologists, using the clinical criteria of Maher and Lees.[8] The disease duration was estimated from history furnished by the patients and other family members and from the medical records.

There were three men and four women with PSP; their ages ranged from 60 to 73 years (mean, 66.4 years). The average duration of symptoms from onset to PET scan was 42.5 months (range, 16 to 72 months).

REPORT OF CASES

CASE 1.—A 67-year-old woman presented with a 36-month history of progressive memory loss, falls, and difficulty in using her hands. Since onset, her mobility, memory, reasoning, and language had deteriorated, and she had developed urinary incontinence 1 year prior to her PET scan. On examination, there was marked perseveration of speech and motor tasks. She had loss of recent memory. Conjugate eye movements were absent in downward and left gaze and impaired in up gaze but complete by vestibulo-ocular maneuver. She had hypomimia, brisk facial reflexes, axial hypertonia, cogwheel rigidity at the wrists, and brisk deep tendon reflexes. The plantar responses were flexor. Computed tomography (CT) of the patient's head showed generalized brain-stem and cortical atrophy.

CASE 2.—A 59-year-old man presented with a 49-month history of progressive imbalance and diplopia. He had a history of impairment in recent memory, dysphagia, and hypophonia. On examination, he had mild recent memory loss. His eye movements were impaired in down gaze by 50%, and up gaze was only possible to the midline. The limitation in gaze could not be overcome by the vestibulo-ocular maneuver. The blink rate was markedly reduced, and the facial reflexes were brisk. He had poor balance and walked with a broad-based gait, with his neck held in retroflexion. The tendon reflexes were brisk. The plantar responses were flexor. Magnetic resonance imaging showed temporoparietal and generalized brain-stem atrophy.

CASE 3.—A 61-year-old man presented with a 37-month history of progressively deteriorating balance, frequent falls, loss of re-

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cent memory, and change in personality. He had difficulty in focusing his vision. On examination, his speech was dysarthric and his recent memory was impaired. He had a 75% limitation in upward and downward gaze and a 25% limitation in horizontal gaze. Saccades were absent vertically and impaired horizontally. Vestibulo-ocular responses were complete in both eyes. The patient's blink rate was less than one per minute, and he had hypomimia. His axial tone was normal. All his tendon reflexes were brisk. The plantar responses were flexor, and there was minimal hand ataxia. Magnetic resonance imaging showed predominant brain-stem atrophy.

Case 4.—A 62-year-old woman presented with a 16-month history of frequent falls. On examination, there was no evidence of dementia. Her vertical conjugate eye movements were absent and horizontal movements impaired, with gaze-evoked horizontal nystagmus. She had mild cogwheel rigidity at her wrists and increased axial tone. Her gait was wide based and she could not walk tandem. Her reflexes were normal. Magnetic resonance imaging showed prominent temporal atrophy, with midbrain and pontine atrophy. At the time of her PET scan, she was least affected and was symptomatic for the shortest duration compared with other patients. Two years after the PET scan, her illness had progressed with the development of marked parkinsonian features, dysarthria, and dysphagia without dementia. She declined a second PET scan.

Case 5.—A 69-year-old woman presented with a 72-month history of frequent falls, dysarthria, and diplopia. On examination, she had impaired recent memory and acalculia. Her upward and downward gaze were impaired, and there was abduction nystagmus in both eyes. Conjugate eye movements were slow in all directions, especially downward. Vestibulo-ocular response was improved only in the upward direction. The blink rate was one per minute. She had hypomimia and brisk facial reflexes with an increased jaw jerk. Her axial tone was increased. Cogwheel rigidity was present in all limbs, and she had marked bradykinesia. The tendon reflexes were normal, and the plantar responses were flexor. Magnetic resonance imaging showed generalized cortical and midbrain atrophy.

Case 6.—A 73-year-old woman presented with a 40-month history of frequent falls, diplopia, and hand tremor. On examination, there was no evidence of dementia. Her vertical gaze was restricted, but her horizontal eye movements were full. Her saccadic eye movements were slow, and she had to use excessive neck movements to look to either side. Her vestibulo-ocular response improved the range of her vertical eye movements. Cogwheel rigidity was present at the wrists, and the axial tone was increased. She had a resting hand tremor with ataxia of the left arm and an ataxic gait. The tendon reflexes were exaggerated with equivocal plantar responses. Magnetic resonance imaging showed generalized cortical and brain-stem atrophy.

Case 7.—A 72-year-old man presented with a 48-month history of a slow shuffling gait and frequent falls. Subsequently, he developed profound memory loss, dysphasic speech, urinary incontinence, and lack of spontaneity. On examination, he had profound dementia. Vertical gaze was restricted, pursuit was broken, and saccadic eye movements were slow. The vestibulo-ocular response was normal. The blink rate was two per minute. Axial tone was increased, and cogwheel rigidity was present at both wrists. Tendon reflexes were exaggerated with extensor plantar responses. Magnetic resonance imaging showed generalized cortical and brain-stem atrophy.

Patients 2, 3, 5, 6,and 7 were taking levodopa-carbidopa (Sinemet); patients 3 and 5 were also taking bromocriptine. Patients 1 and 4 had stopped all treatment because of poor response. There was no clinical improvement noted among the patients who were taking medication. None of the patients were taking neuroleptics prior to their PET scan.

Seven age-matched controls underwent PET scans. The controls were neurologically normal and not taking any medication. The ages of the controls ranged from 57 to 73 years (mean, 65.5 years). The individual ages of the controls and patients differed by a maximum of 3 years.

METHODS

We used a PET protocol that has been approved by the University of British Columbia, Vancouver, Canada. All medications were withdrawn the night before the scan. Positron-emitting fluorine 18 was incorporated into a dopa derivative to produce 6-FD using a cyclotron (TRIUMF CP-42), as described elsewhere.[9,10] The PET studies were performed with the University of British Columbia TRIUMF PETT VI system.[11] This apparatus permits emission data to be collected simultaneously from seven contiguous axial slices, with a center-to-center slice separation of 14 mm, an average axial resolution of approximately 11-mm full width at half maximum, and an in-plane resolution averaging 9.2-mm full width at half maximum. All patients underwent a magnetic resonance imaging scan scan (Picker 0.15-T magnet), except for patient 1 who underwent a CT scan. Magnetic resonance imaging or CT was performed to locate the plane of the striatum. This plane was identified and marked above the orbitomeatal line with a pair of laser beams. The patient was then positioned so that the magnetic resonance imaging or CT plane that best visualized the striatum corresponded to the fifth PET slice.

One hour before the scan, 100 mg of carbidopa was administered orally. This dose of carbidopa prevents peripheral decarboxylation of labeled dopa.[12] During scanning, the patient lay supine with head movements limited by a molded thermoplastic face mask. A transmission scan was performed prior to tracer administration to permit attenuation correction to be applied to the emission data. Each subject received 74 to 129.5 MBq of 6-FD. Twelve sequential emission scans, each lasting 10 minutes, were performed, starting immediately after tracer administration.

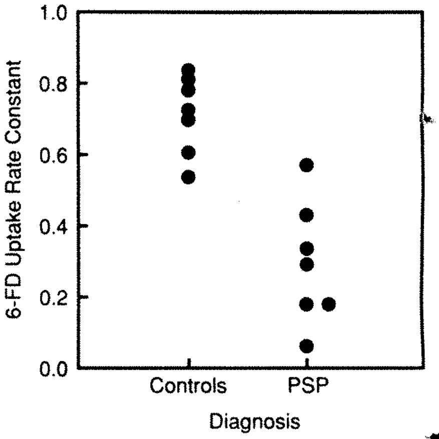

Fig 1.—The individual 6-[^{18}F]fluoro-L-dopa (6-FD) uptake rate constants of the patients with progressive supranuclear palsy (PSP) and the controls are compared. As a group, patients with PSP had significantly reduced uptake rate constants compared with age-matched controls (PSP group mean[SD], 0.29[0.181]; controls, 0.71[0.099]; $P<.001$).

Sequential blood samples were obtained in each subject via an indwelling radial artery catheter, and the total plasma radioactivity was measured in each sample. The relationship between plasma 6-FD radioactivity and radioactive metabolites vs time was calculated.[13] Striatal regions of interest with an area of 12 cm^2 were placed on all slices in which striatal radioactivity was evident in excess of the background. Two cortical regions of interest occupying an area of 9 cm^2 were placed in the posterior temporoparietal cortex. Tissue and plasma measurement were analyzed by a graphic method as described previously.[4]

To minimize the partial volume effect due to striatal atrophy, we used large regions of interest to sample the whole striatum. Radioactivity in small structures may be underestimated owing to the partial volume effect, as the counts are distributed over a larger area. Despite a wide distribution, however, counts are conserved.[14] Therefore, a large region of interest will measure total radioactivity in the structure of interest.[4]

RESULTS

The 6-FD uptake constant among the PSP group was significantly reduced (PSP group mean[SD], 0.29[0.181]; controls, 0.71[0.099]; $P<.001$, *t* test), compared with that among controls (Fig 1). The uptake constant among the patients with PSP correlated inversely with the duration of symptoms ($r=.85$; $P=.015$) (Fig 2).

The magnetic resonance imaging and CT features of these patients conformed to previously reported criteria for the diagnosis of PSP.[15]

COMMENT

We found significantly reduced 6-FD uptake rate constants in patients with PSP compared with age-matched controls. The reduction correlated with the duration of the disease. Our results im-

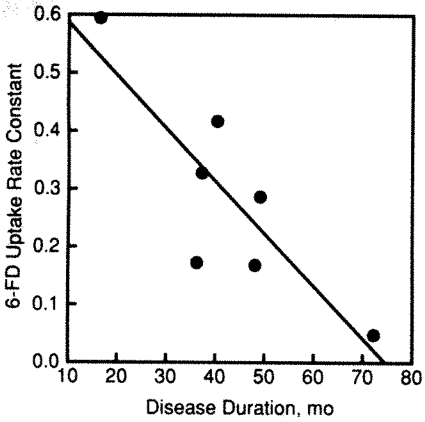

Fig 2.—The 6-[^{18}F]fluoro-L-dopa (6-FD) uptake rate constant for the patients with progressive supranuclear palsy is plotted as a function of disease duration ($r = .85$; $P = .015$).

ply presynaptic nigrostriatal dopaminergic loss and are consistent with those in previous reports.[16] Our findings are in accord with the neuropathologic changes and the severe dopaminergic loss on neurochemical examination of the nigrostriatal pathway in PSP.[1,3,17-19]

Although presynaptic dopaminergic input almost certainly plays an important role in the parkinsonian manifestations in PSP, postsynaptic dopaminergic receptors are also known to be affected in the disease process.[20-22] Baron et al[21] have shown reduced tritiated spiperone binding in early and late cases of PSP. Similarly, a poor therapeutic response in all our patients early in the disease indirectly suggests early involvement of the postsynaptic dopaminergic nigrostriatal system. The parkinsonism in patient 4, who had normal findings on PET and the shortest duration of symptoms, further suggests that there may be postsynaptic dysfunction early in the disease. Alternatively, there could be a defect in dopa synthesis, which would not be detected by PET with 6-FD.

We have found reduced 6-FD uptake rate constants in early idiopathic parkinsonism (unpublished data, 1985). In contrast, the uptake rate constant was normal in our patient with early parkinsonism due to PSP. This suggests that there may be relatively minor presynaptic dopaminergic loss at the time of onset of symptoms in PSP. Since the mean interval from onset of symptoms to diagnosis of PSP is 3.9 years,[8] most patients already have established nigrostriatal dopaminergic loss at the time of diagnosis. In such patients, clinical features may relate to combined presynaptic and postsynaptic dopaminergic dysfunction.

Along with the widespread cholinergic deficit[19] and the reduced frontal lobe glucose utilization,[16,23,24] depressed dopaminergic input to the caudate nucleus has been implicated in the dementia of PSP.[18] Our findings in patients 4 and 6, who had normal mental status and the least affected striatal 6-FD uptake (compared with the rest of the patients), are consistent with the concept that deficient dopaminergic input to the striatum may play a role in the dementia of PSP.[18]

Atypical clinical manifestations in patients with PSP are well recognized.[25] A larger study combining careful clinical evaluation with presynaptic and postsynaptic PET studies of the nigrostriatal pathway would help to elucidate the pathophysiologic processes of PSP.

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References

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy: a heterogeneous degeneration involving the brain stem, basal ganglia, and cerebellum with vertical gaze and pseudobulbar palsy, nuchal dystonia, and dementia. *Arch Neurol.* 1964;10:333-359.

2. Richardson JC, Steele JC, Olszewski J. Supranuclear ophthalmoplegia, pseudobulbar palsy, nuchal dystonia and dementia: a clinical report on eight cases of 'heterogeneous system degeneration.' *Trans Am Neurol Assoc.* 1963;88:25-29.

3. Steel JC. Progressive supranuclear palsy. *Brain.* 1972;95:693-704.

4. Martin WRW, Palmer MR, Patlak CS, Calne DB. Nigrostriatal function in humans studied with positron emission tomography. *Ann Neurol.* 1989;26:535-542.

5. Leenders KL, Palmer AJ, Quinn N, et al. Brain dopamine metabolism in patients with Parkinson's disease measured with positron emission tomography. *J Neurol Neurosurg Psychiatry.* 1986;49:853-860.

6. Martin WRW, Stoessl AJ, Adam MJ, et al. Positron emission tomography in Parkinson's disease: glucose and dopa metabolism. In: Yahr MD, Bergmann KJ, eds. *Advances in Neurology: Parkinson's Disease.* New York, NY: Raven Press; 1986;45:95-101.

7. Nahmias C, Garnett ES, Firnau G, Lang A. Striatal dopamine distribution in parkinsonian patients during life. *J Neurol Sci.* 1985;69:223-230.

8. Maher ER, Lees AJ. The clinical features and natural history of the Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). *Neurology.* 1986;36:1005-1008.

9. Ruth TJ. The production of ^{18}F-F$_2$ and ^{15}O-O$_2$ sequentially from the same target chamber. *Int J Appl Radiat Isot.* 1988;36:1203-1206.

10. Adam MJ, Jivan S. Synthesis and purification of L-[^{18}F]6-fluorodopa. *J Appl Radiat Isot.* 1988;39:1203-1206.

11. Evans B, Harrop R, Heywood D, et al. Engineering development on the UBC-TRIUMF modified PETT VI positron emission tomography. *IEEE Trans Nucl Sci.* 1983;NS-30:707-710.

12. Rao SK, Calne DB. Studies with carbidopa (MK 486). In: Calne DB, ed. *Advances in Neurology: Progress in the Treatment of Parkinsonism.* New York, NY: Raven Press; 1973;3:73-77.

13. Boyes BE, Cumming P, Martin WRW, McGeer EG. Determination of plasma [^{18}F]-6-fluorodopa during positron emission tomography: elimination and metabolism in carbidopa-treated subjects. *Life Sci.* 1986;39:2243-2252.

14. Hoffman EJ, Phelps ME. Positron emission tomography: principles and quantitation. In: Phelps ME, Mazziotta JC, Schelbert HR, eds. *Positron Emission Tomography and Autoradiography.* New York, NY : Raven Press; 1986:237-286.

15. Schonfeld SM, Golbe LI, Sage JI, et al. Computed tomographic findings in progressive supranuclear palsy: correlation with clinical grade. *Mov Disord.* 1987;2:263-278.

16. Leenders KL, Frackowiak SJ, Lees AJ. Steele-Richardson-Olszewski Syndrome: brain energy metabolism, blood flow and fluorodopa uptake measured by positron emission tomography. *Brain.* 1988;111:615-630.

17. Jellinger K, Riederer P, Tomonaga M. Progressive supranuclear palsy: clincopathological and biochemical studies. *J Neural Transm.* 1980;16:111-128.

18. Kish SJ, Chang LJ, Mirchandani L, Shannak K, Hornykiewicz O. Progressive supranuclear palsy: relationship between extrapyramidal disturbances, dementia, and brain neurotransmitter markers. *Ann Neurol.* 1985;18:530-536.

19. Ruberg M, Javoy-Agid F, Hirsch E, et al. Dopaminergic and cholinergic lesions in progressive supranuclear palsy. *Ann Neurol.* 1985:18:523-529.

20. Pierot L, Desnos C, Blin J, et al. D1- and D2-type dopamine receptors in patients with Parkinson's disease and progressive supranuclear palsy. *J Neurol Sci.* 1988;86:291-306.

21. Baron JC, Maziere B, Loch C, Sgouropoulos P, Bonnet AM, Agid Y. Progressive supranuclear palsy: loss of striatal dopamine receptors demonstrated in vivo by positron tomography. *Lancet.* 1985;1:1163-1164.

22. Bokobza B, Ruberg M, Scatton B, Jovoy-Agid F, Agid Y. [^{3}]Spiperone binding, dopamine and HVA concentration in Parkinson's disease and supranuclear palsy. *Eur J Pharmacol.* 1984;99:167-175.

23. D'Antona R, Baron JC, Samson Y, et al. Subcortical dementia: frontal cortex hypometabolism detected by positron tomography in patients with progressive supranuclear palsy. *Brain.* 1985;108:785-799.

24. Foster NL, Gilman S, Berent S, Hichwa RD. Distinctive patterns of cerebral cortical glucose metabolism in progressive supranuclear palsy and Alzheimer's disease studied with positron emission tomography. *Neurology.* 1986;36(suppl 1):338.

25. Davis PH, Bergeron C, McLachlan DR. Atypical presentation of progressive supranuclear palsy. *Ann Neurol.* 1985;17:337-343.

Idiopathic Intracranial Hypertension Without Papilledema

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• We describe 10 patients with idiopathic intracranial hypertension who did not have papilledema. Idiopathic intracranial hypertension without papilledema, although rarely reported, may well be a clinically important headache syndrome. Historical and demographic features of patients with idiopathic intracranial hypertension without papilledema are similar to those of patients with papilledema. Obese women with chronic daily headache and symptoms of increased intracranial pressure, pulsatile tinnitus, history of head trauma or meningitis, an empty sella on imaging studies, or a headache that is unrelieved by standard therapy should have a diagnostic lumbar puncture. Findings from laboratory and neurologic investigations are normal in most patients with idiopathic intracranial hypertension without papilledema. Initial management should include removal of possible inciting agents, weight loss if applicable, and standard headache therapy. Lumbar puncture and diuretic therapy should precede a trial of corticosteroids. Surgery (lumboperitoneal or ventriculoperitoneal shunt or perhaps optic nerve sheath fenestration) may be indicated for prolonged incapacitating headache that is not responsive to medical management or lumbar puncture.

(*Arch Neurol.* 1991;48:392-399)

Idiopathic intracranial hypertension (IIH), also known as pseudotumor cerebri or benign intracranial hypertension, is characterized by headache, increased intracranial pressure, and papilledema. In patients with this condition, results of the neurologic examination are normal, except for an occasional sixth nerve palsy. Findings from neuroradiologic investigations are usually normal but may show small ventricles or an empty sella.[1-8] Pseudotumor cerebri was originally described by Quincke[9] in 1897, with bilateral papilledema as the cardinal physical sign. However, in 1972, Lipton and Michelson[10] reported the first case of benign intracranial hypertension without papilledema, and since 1972, several authors have reported IIH with unilateral,[11] asymmetric,[12] or no[13,14] papilledema.

We describe a series of 10 patients with IIH who did not have papilledema.

MATERIALS AND METHODS

All 10 patients were referred for neurologic evaluation of headache between 1977 and 1990. We obtained histories directly from the patient and chart review. We emphasized the character, location, duration, frequency, and associated headache symptoms, and we reviewed possible inciting conditions.[15]

All patients underwent complete general, neurologic, and ophthalmoscopic examinations. We recorded age, sex, weight, blood pressure, ophthalmoscopic findings, visual fields, and evidence of head trauma. Seven patients had endocrinologic consultation for obesity or menstrual irregularities. Laboratory studies included an automated chemistry profile, complete blood cell count with differential cell count, and tests for prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and rapid plasma reagin. Endocrinologic laboratory studies on seven patients included determinations of serum prolactin, follicle-stimulating hormone, luteinizing hormone, corticotropin, triiodothyronine (resin uptake) thyroxine, thyrotropin, and cortisol levels. Urine samples for 24-hour free cortisol, 17-hydroxysteroids, 17-ketosteroids, and 17-ketogenic steroids were obtained from five patients.

All patients had a computed tomographic (CT) or magnetic resonance imaging (MRI) scan of the head done, or both; all patients also had single or multiple lumbar punctures (LPs) done. All LPs were performed by the same operator (S.D.S.).

The patient was positioned in the lateral decubitus position on a level surface, with the knees extended and neck and sagittal sinus on the same plane as the spinal canal. A No. 18- or 20-gauge spinal needle was introduced at the L4-5 spinal level; the manometer was positioned at a 90° angle to the spinal canal. The opening pressure was recorded with the use of a standard manometer that was connected to the spinal needle by sterile tubing, with the patient relaxed and breathing easily.

REPORT OF CASES

Tables 1 and 2 give the histories, findings from physical examinations and other investigations, and treatment and follow-up of patients with IIH who did not have papilledema. We report the following three illustrative cases regarding this condition.

CASE 2.—A 40-year-old woman was originally seen in 1989, with a 3-year history of daily headaches. These headaches were continuous, severe, and pounding; worse in the morning; usually localized to the right orbit and temple, but at times bilateral; and associated with nausea, depression, and sleep disturbance. Her medical history revealed irritable bowel syndrome and dysmenorrhea.

On examination, the patient was obese (75 kg, 155 cm) and normotensive. Results of a neurologic examination were normal. Neuro-ophthalmologic examination demonstrated a visual acuity of 20/30 OU and normal visual fields. Ophthalmoscopic examination revealed no papilledema, a benign nevus, and spontaneous venous pulsations. A fluorescein angiogram was normal.

The opening pressure on LP was 330 mm of cerebrospinal fluid (CSF). A CT scan and an MRI scan showed an empty sella with normal-sized, but slightly asymmetric, ventricles. Results of routine laboratory and endocrine studies, including determination of serum prolactin, luteinizing hormone, follicle-stimulating hormone, and urinary 17-hydroxysteroid and 17-ketogenic steroid levels, were normal. The CSF composition, VDRL, and cultures were negative.

Before our evaluation, treatment modalities included intravenous morphine sulfate drip, cyproheptadine hydrochloride, β-adrenergic blockade, calcium channel blockade, tricyclic antidepressants, phenelzine sulfate, lithium carbonate, methylprednisolone acetate, phenytoin sodium, and biofeedback.

At admission to Germantown Hospital, Philadelphia, Pa, the patient was being treated with meperidine hydrochloride, propranolol hydrochloride, lithium carbonate, and clonazepam. She was detoxified from the narcotics. Lithium carbonate, which has been implicated in producing IIH, and β-adrenergic blockers were discontinued.

Sequential treatment with dihydroergotamine mesylate, steroids, and loop diuretics provided minimal relief. An LP relieved the patient's headaches for 4 to 7 hours. In October 1989, she had a ventriculoperitoneal shunt, which brought immediate headache relief. By January 1990, she had only occasional migraine headaches that were relieved with dihydroergotamine, and she returned to work (after being disabled for 2 years).

CASE 3.—In December 1986, a 43-year-old woman with a history of syncope, subarachnoid hemorrhage, cataracts, coronary artery disease, hypertension, and obesity was reexamined for a 1-year history of daily headache.

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Reprint requests to Germantown Neurological Associates, 1 Penn Blvd, Philadephia, PA 19144 (Dr Silberstein).

The headache, noted on awakening, was bifrontal, dull, and achy, and it associated with pulsatile tinnitus, dizziness, and sleep disturbance.

The patient was originally admitted to Germantown Hospital in November 1979, with the acute onset of severe occipital headache and neck pain and stiffness. Subarachnoid hemorrhage was diagnosed. The CSF was grossly bloody. A CT scan and cerebral arteriogram were normal. She was treated with intravenous dexamethasone sodium phosphate and antihypertensive medication. Follow-up LPs showed clearing of CSF. Repeated CT scans remained normal. She had no neurologic sequelae, except for daily headache. After discharge, the headaches were controlled with diuretics, β-adrenergic blockers, and tapering doses of steroids. Steroids were discontinued in June 1980. In February 1981, she had visual loss in the right eye from a dense cataract.

In December 1986, examination disclosed a notable finding for obesity (104 kg, 160 cm) and 2/6 systolic flow murmur. Results of neurologic examination were normal. Ophthalmologic examination demonstrated a dense right cataract; visual acuity was 20/20 OS, with light perception in the right eye. Papilledema was absent; spontaneous venous pulsations were present. A fluorescein angiogram was normal.

In December 1986, an LP showed an opening pressure of 270 mm of CSF. The CSF composition, cultures, and VDRL were normal, except for a low protein level (0.13 g/L). Findings from routine and endocrinologic laboratory studies were normal, as were a CT scan and an electroencephalogram.

Sequential use of β-adrenergic blockers, diuretic therapy, methylprednisolone, and serial LPs decreased the severity of headache. In March 1990, the patient's LP showed an opening pressure of 260 mm of CSF. The headache was promptly relieved by LP, but recurred in weeks to months.

Case 10.—A 46-year-old woman was originally seen at Germantown Hospital in May 1986. Headaches, which she had had since the age of 6 years, had gradually increased in severity and frequency during the 3 years before examination. They occurred five to six times each week and lasted 3 to 4 hours. They were pulsating, located in the left orbit and temple, precipitated by sunlight, and associated with nausea. In addition, she had continuous daily headaches, similar in location but less intense, which were present in the morning. Her medical history was significant for hypothyroidism that required daily levothyroxine sodium supplementation (0.2 mg).

At examination, the patient was obese (82.6 kg, 172.7 cm), normotensive (150/84 mm Hg), and clinically euthyroid. Results of a neurologic examination were normal. Ophthalmologic examination revealed a visual acuity of 20/40 OU, normal visual fields, spontaneous venous pulsations, and no papilledema. A fluorescein angiogram was normal. A CT scan and MRI scan of the head and electroencephalogram were normal.

From 1986 through 1989, the patient was treated with oral ergotamine tartrate preparations, calcium channel antagonists, tricyclic antidepressants, monoamine oxidase inhibitors, β-blockers, and nonsteroidal anti-inflammatory agents. She was most recently treated with methylprednisolone, but her headache recurred when the dose was tapered.

An LP was performed in March 1990. The opening pressure was 255 mm of CSF. The CSF composition, cultures, and VDRL were normal. Headache was completely and promptly relieved following LP.

On follow-up, corticosteroids were discontinued, and diuretic therapy was started. The patient usually had headache-free periods that lasted from 2 days to 2 weeks, with a repeated LP yielding immediate relief.

RESULTS

Ten patients with intracranial hypertension without papilledema were examined from 1977 to 1990 (Tables 1 through 3).

Historical and Clinical Features

All patients had chronic daily headache with migrainous features (Table 3). The headache was bilateral in five of 10 patients and pulsating in eight of 10. All 10 patients had severe, daily, continuous headaches; all headaches lasted for greater than 2 weeks. Four patients had pulsatile tinnitus. All patients had headaches on awakening; nine of 10 had nausea or vomiting. Two patients had headaches that worsened on coughing or on Valsalva's maneuver.

The mean duration of symptoms before diagnosis was 76.2 months (range, 3 to 252 months; median, 36 months). Three patients had a history of significant head trauma. One patient had had meningitis, and one patient had had a subarachnoid hemorrhage. Four patients had controlled hypertension. Six of eight women had menstrual irregularities. Two patients were being treated with thyroid hormone replacement for primary hypothyroidism. One woman was taking replacement estrogens (estrogen/progesterone cycled), and one woman was receiving chronic steroid therapy for Still's disease.

The patients ranged in age from 26 to 46 years (mean age, 37.5 years). Eight of the 10 patients were women. Eight patients were obese (>25% above ideal body weight) by Metropolitan Life Insurance Company tables of ideal weight for height.[16] Results of neurologic examinations were normal in all patients (Table 1).

Ocular Examinations

All patients underwent formal ophthalmologic examinations (Table 1). One patient had pseudopapilledema with buried drusen, and one patient had a benign retinal nevus. Findings from visual field studies were normal in all but two patients. One patient had a dense cataract with only light perception in the affected eye, and one patient had a bilateral superior altitudinal field defect. None of the patients had papilledema, exudates, hemorrhages, an enlarged blind spot, elevated intraocular pressure, or abnormal pupillary responses. Spontaneous venous pulsations were present in all but one patient. Fluorescein angiograms were normal in the seven patients who were tested.

Laboratory Findings

Findings from routine laboratory studies were normal for all patients; these studies included tests for antinuclear antibody, rheumatoid factor, erythrocyte sedimentation rate, and rapid plasma reagin. Also, findings from endocrinologic laboratory investigations for obesity or menstrual irregularities were normal in five of seven patients who were studied. Two patients had a slightly elevated serum cortisol level, but it was appropriately suppressed with dexamethasone acetate, and corticotropin levels were normal.

All patients underwent a CT or MRI scan of the head, or both. Seven had completely normal study results. Two patients had an empty sella, and one patient had symmetrically small ventricles. There was no evidence of an intracranial mass or hydrocephalus in any patient.

The CSF composition was normal, except for three patients with decreased CSF protein levels. The opening pressure on LP ranged from 230 to 450 mm of CSF; only one nonobese patient had an opening pressure less than 250 mm of CSF.

Treatment

All patients received standard headache therapy, including β-adrenergic antagonists, calcium channel antagonists, narcotic and nonnarcotic analgesia, enteral and parenteral ergotamine preparations, phenytoin, carbamazepine, fluoxetine, monoamine oxidase inhibitors, tricyclic antidepressants, lithium carbonate, cyproheptadine, *or* oxygen therapy at some point in their treatment (Table 2). Partial or temporary headache relief was attained; however, recurrence was the rule. All patients subsequently received trials of furosemide, acetazolamide sodium, or corticosteroids (dexamethasone/prednisone).

Three patients required surgical intervention when medical therapy failed to relieve headache. Two patients had a ventriculoperitoneal shunt; the other patient had a lumboperitoneal shunt.

All operations successfully eliminated incapacitating headache.

Follow-up

Of the seven patients who were treated with medical therapy and LP, one died, and six had intermittent severe headaches that required an LP and removal of CSF periodically to relieve symptoms (Table 2).

Patients were followed up for 2 months to 10 years. At subsequent examinations, papilledema had not developed in any of the patients.

COMMENT

Idiopathic intracranial hypertension without papilledema is rarely reported but may well be a clinically important syndrome. Our patients, except for the absence of papilledema, fit the following accepted criteria for IIH with papilledema[1-7] (Table 4):

1. Headache: Chronic tension-type headache with migrainous features is always present on awakening and associated with pulsatile tinnitus.
2. Patients: They are predominantly obese women aged 20 to 50 years.
3. History: Head trauma, meningitis, or subarachnoid hemorrhage are not uncommon.
4. Examinations: Physical and neurologic examination results are within normal limits, except for obesity and mild hypertension. No papilledema is present, but there may be a sixth nerve palsy.
5. LP: Lumbar puncture demonstrates increased CSF pressure with a normal composition (may show a decreased protein level).
6. Neuroradiology: The CT or MRI scans show no evidence of an intracranial mass or hydrocephalus (an empty sella may be present).

The patients had an elevated CSF pressure and essentially a normal CSF composition. Neuroradiologic studies showed an empty sella in two patients and small ventricles in one patient. Neuro-ophthalmologic examinations revealed pseudopapilledema with buried drusen in one patient. Along with IIH, chronic daily headache, female predominance, obesity, young age, normal laboratory study findings, or an empty sella were common findings in our patients (Tables 5 through 8).[17-23]

Pulsatile tinnitus was present in four of our patients. In a prospective study (conducted in 1987), Sismanis[24] found pulsatile tinnitus in each of 20 patients with classic pseudotumor cerebri. Wall and George,[25] in 1989, prospectively found that 60% of a group of patients with IIH had pulsatile tinnitus. The mechanism for this is thought to be vascular pulsation in CSF secondary to intracranial hypertension that is transmitted to the walls of the venous sinuses.[24]

Table 1.—History,

Patient/ Age, y/Sex	History Medical Conditions	Medications on Evaluation†	Irregular Menses	Head Trauma/Meningitis
1/41/M	HTN, SZ, SYN	–	NA	Meningitis, beaten
2/40/F	IBS	–	+	–
3/43/F	HTN, CAD, SYN	–	–	+, SAH
4/33/F	MVP, Depr	–	+	–
5/26/M	–	–	NA	–
6/35/F	SZ	–	+	+, MVA/fall
7/33/F	HTN	BCPs	+	–
8/41/F	HTN, Thyr, Depr	Levothyroxine	+	+, MVA/fall
9/37/F	Still's disease, PUD	Prednisone	+	–
10/46/F	Thyr	Prednisone	–	–

There was a history of head trauma, meningitis, or subarachnoid hemorrhage in four of our patients. In 1980, Spence et al[14] reported that seven of nine patients with benign intracranial hypertension without papilledema had a history of head trauma. Traumatic subarachnoid hemorrhage or meningeal irritation with impairment of CSF flow might account for the elevated intracranial pressure in these patients.

All of our patients had a chronic daily headache present on awakening; this headache was frequently aggravated by analgesic or narcotic overuse (Table 3). The continuous chronic daily headache was often associated with more severe, intermittent, migrainous headaches. This might be a different variety of transformed or evolutative migraine, perhaps induced by weight gain. The quality of the pain varied from a dull ache to sharp and throbbing; however, most patients had a pulsating headache associated with nausea and vomiting (Table 9).

The mean duration of symptoms before diagnosis was 76.2 months (median, 36 months) compared with 3 to 5 months for patients with IIH.[18] The prolonged duration of symptoms may reflect a delay in performing an LP in patients with normal findings from neuroradiologic investigations and examinations. Our early patients had LPs done to rule out subarachnoid hemorrhage or meningitis following a change in the character or severity of their daily headache. Four patients had LPs performed after failure of maximal medical therapy. More recently, as a typical demographic and headache profile has emerged, we have been performing LPs earlier in the course of the illness (Table 10).

The headache of increased intracranial pressure is poorly defined, probably a reflection of the many causes of increased intracranial pressure, such as IIH, hydrocephalus, intracranial infections, and intracranial neoplasms. Wall[26] recently described the headache profile of 58 patients with IIH (Table 4). Severe, daily, throbbing, or pulsating pain associated with nausea, vomiting, hysical Examination, and Investigations*

Physical Findings						Investigations			
			Ophthalmologic Findings			Lumbar Puncture			
Obesity (+), ht/wt % > IBW‡	BP, mm Hg	General and Neurologic Examination	Fundi	Visual Fields	Fluorescein Angiogram	OP, H_2O	Composition§	MRI/CT	LABS‖
+, 55	170/110	WNL	±SVP	WNL	ND	450	WNL	WNL	WNL
+, 25	110/60	WNL	Nevus	WNL	WNL	370	WNL	Empty sella lateral ventricle asymmetry	WNL
+, 49	150/80	WNL	WNL	L, WNL; R¶, light perception	WNL	270	CSF Protein 0.13 g/L	WNL	WNL
−	90/60	WNL	WNL	WNL	WNL	230	CSF Protein 0.18 g/L	Mild cortical atrophy	Increased cortisol level
−	134/80	WNL	Buried drusen	WNL	WNL	280	WNL	WNL	WNL
+, 100	114/82	WNL	WNL	WNL	WNL	320	WNL	Small ventricles	Increased cortisol level
+, 42	130/80	WNL	WNL	WNL	ND	340	WNL	Empty sella	WNL
+, 45	114/70	WNL	WNL	WNL	WNL	310	WNL	WNL	WNL
+, 31	124/90	WNL	WNL	Bilateral superior temporal field defect	ND	370	WNL	WNL	WNL
+, 24	150/84	WNL	WNL	WNL	WNL	280	WNL	WNL	WNL

*Plus sign indicates present; minus sign, no, none, or negative; ht/wt, height/weight; IBW, ideal body weight; BP, blood pressure; LP, lumbar puncture; OP, opening pressure; MRI, magnetic resonance imaging; CT, computed tomography; LABS, laboratory studies; HTN, hypertension; SZ, seizure; SYN, syncope; NA, not applicable; WNL, within normal limits; SVP, spontaneous venous pulsations; ND, not done; IBS, irritable bowel syndrome; CAD, coronary artery disease; SAH, subarachnoid hemorrhage; CSF, cerebrospinal fluid; MVP, mitral valve prolapse; Depr, depression; MVA, motor vehicle accident; BCPs, birth control pills; Thyr, hypothyroid; and PUD, peptic ulcer disease. All patients underwent ophtho/neuro-opthalmologic evaluations; no patient had papilledema.

†Medications associated with elevated intracranial pressure.

‡Percentage above IBW (% > IBW) with the use of the Metropolitan Age/Weight/Height tables.[16]

§Cerebrospinal fluid composition included cultures, VDRL, and determinations of protein and glucose values and cell counts. Only abnormal values are noted.

‖Laboratory studies included a complete blood cell count with a differential cell count, automated chemistry profile, and determinations of erythrocyte sedimentation rate, antinuclear antibody, rheumatoid factor, and triiodothyronine (routine urinalysis), thyroxine, thyrotopin (thyroid-stimulating hormone), and corticotropin values.

¶Right dense cataract.

and pulsatile tinnitus were common in his patients and in our series. Our patients' headache profile most closely approximates the combination of migraine and chronic tension-type headache as defined by International Headache Society classification.[27]

The frequency of IIH is about one case per 100 000 per year, or 19.3 in obese women aged 20 to 44 years.[17] Idiopathic intracranial hypertension without papilledema probably occurs in a subset of these patients and therefore would be expected to occur less frequently than 19.3/100 000 in women aged 20 to 44 years.[17] Ten to fifty percent of patients with brain tumors and increased intracranial pressure, proved by LP, may not have papilledema.[28] A prospective analysis of patients with typical demographic and clinical features of IIH without papilledema may further define the incidence of this entity.

Two of our patients had an empty sella as shown on a CT scan. Primary empty-sella syndrome is due to extension of the subarachnoid space through an incompetent diaphragma sellae, and increased intracranial pressure is thought to be a factor in its development. Papilledema is less frequent in patients with IIH with an empty sella. In the series of of Foley and Posner,[20] 50% of patients with increased intracranial pressure and an empty sella did not have papilledema. Thus, patients with chronic daily headache and an empty sella may have increased intracranial pressure even without papilledema.

The role of prolonged CSF pressure monitoring in diagnosis and management of IIH without papilledema is controversial. Twenty-four–hour CSF pressure monitoring was used in seven patients without papilledema to document abnormal pressure waves and increased intracranial pressure.[14] The greatest usefulness of this technique may be in monitoring selected patients whose CSF pressure by LP is normal or borderline elevated and who demonstrate headache relief after removal of CSF.

There is absolutely no evidence that IIH without papilledema is a threat to vision.[29-32] All but two of our patients had normal visual acuity and visual fields. One patient had pseudopapilledema with buried drusen, and the other patient had bilateral superior field defects. To our knowledge, these defects are nonspecific and not related to IIH. Ophthalmoscopic examinations done from 3 months to 2½ years after a first visit have not shown papilledema.

The presence of spontaneous retinal venous pulsations usually signifies normal intracranial pressure. Walsh et al[28] found that the mean pressure for obliterating spontaneous retinal venous pulsations was 200 mm of CSF. All but one of our patients had venous pulsations despite elevated intracranial pressure. The mechanism, which prohibits the development of papilledema in our patients, may also prevent the loss of venous pulsations despite elevated CSF pressure.

We believe that IIH should be considered even in the absence of papilledema. Patients with chronic daily headache, even if complicated by analgesic rebound, may benefit from LP early in the course of their illness. Increased intracranial pressure should be looked for, especially in women, 20 to 50 years,

Table 2.—Treatment and Follow-up*

	Treatment							
	Medical					Follow-up		
Patient	Standard Headache Therapy	Steroids or Diuretics	Surgery	Outcome	Recurrence	Time, mo	Neurologic	Papilledema
1	Propranolol, phenytoin	Furosemide, hydrodiuril, acetazolamide	None	Temporary relief with LP	1-2/mo	52†	WNL	None
2	Propranolol, dihydroergotamine, morphine sulfate, cyproheptadine, hydrodiural, tricyclic antidepressant, phenytoin, phenylzine	Furosemide	Ventriculoperitoneal shunt 10/89	Relief	No	7	WNL	None
3	Propranolol	Furosemide, acetazolamide, prednisone	None	Relief with LP	1-2/mo	120	WNL	None
4	Dihydroergotamine, calcium channel blocker (verapamil/nifedipine), fluoxetine, bromocryptine, depakote	Furosemide	None	Relief with dihydroergotamine/diuretic	2/mo	36	WNL	None
5	Calcium channel blocker (verapamil/nifedipine), dihydroergotamine	Furosemide, acetazolamide, dexamethasone	Lumboperitoneal shunt	Relief	No	24	WNL	Pseudopapilledema
6	Phenytoin, fluoxetine	Furosemide, dexamethasone	None	Intermittent recurrent headache	1-2/wk	30	WNL	None
7	Propranolol, fluoxetine	Furosemide	None	Temporary relief with LP	1-2/mo	108	WNL	None
8	Propranolol, dihydroergotamine, methysergide, fluoxetine, calcium channel blocker (verapamil/nifedipine), phenytoin, phenylzine	Acetazolamide	Ventriculoperitoneal shunt, 1/90	Low-pressure headache relief	No	2	WNL	None
9	. . .	Dexamethasone	None	Temporary relief with LP	1/6 mo	6	WNL	None
10	Tricyclic antidepressant, propranolol, phenylzine, fluoxetine	Prednisone, furosemide	None	Relief with LP and diuretic	1-2/mo	48	WNL	None

*LP indicates lumbar puncture; WNL, within normal limits. All LPs showed positive findings for all patients.
†Follow-up until death.

with obesity, pulsatile tinnitus, history of head trauma or meningitis, headache on awakening, presence of an empty sella in imaging studies, or headache that is unrelieved by standard therapy.

Pathophysiology

The pathophysiology of IIH is unknown. Postulated mechanisms include (1) an increased rate of CSF formation, (2) an increased intracranial venous pressure, (3) a decreased rate of CSF absorption, and (4) an increase in brain interstitial fluid (edema). Recent studies have suggested that a decreased rate of absorption at the arachnoid villi and interstitial brain edema are the major contributors.[33-41]

Many mechanisms have been postulated for the absence of papilledema in patients with increased intracranial pressure as follows: (1) bilateral congenital optic nerve sheath defects; (2) bilateral acquired optic nerve sheath defects (subarachnoid hemorrhage, meningitis); (3) "chronic pseudotumor cerebri" with resolution of papilledema; and (4) intermittent elevation of intracranial pressure below the threshold to produce papilledema. Bilateral congenital optic nerve sheath anomalies may explain the absence of papilledema despite elevation of CSF pressure. The CT and MRI scans are normal; however, sensitivity and specificity of imaging in this setting is undetermined.[42-45] Autopsy or surgical documentation of optic nerve sheath defects may be helpful in future investigations.

Our three patients with head trauma and one patient with purulent bacterial meningitis may have had an acquired optic nerve sheath defect. In 1980, Spence et al[14] reported a series of nine patients with IIH without significant papilledema. Seven patients had had previous head trauma. Traumatic subarachnoid hemorrhage or meningeal inflammation with impairment of CSF absorption (and secondary arachnoiditis) may account for the absence of papilledema in the patients described by Spence et al[14] and us.

Chronic pseudotumor cerebri may explain IIH without papilledema.[27,29,46] Corbett et al,[29] in a follow-up study of 57 patients throughout a 5- to 41-year period, found persistent intracranial hypertension despite resolution of papilledema in seven of 10 patients, and half of

Table 3.—Headache Profile*

			Associated Symptoms†				
Location	Quality	Frequency (Duration of Headache)	Nausea/ Vomiting	Photophobia/ Phonophobia	Aura	Pulsatile Tinnitus	Vertigo/ Dizziness
Bilateral vertex	Pulsating	Daily continuous (3 mo)	+	–	–	–	+
Unilateral R orbit	Pulsating	Daily continuous (1 y)	+	–	–	–	–
Bilateral frontal	Pressure	Daily continuous (3 y)	–	–	–	+	+
Bilateral occipital	Pressure	Daily continuous (3 y)	+	–	+	+	+
Unilateral R sided	Pulsating	Daily continuous (2 wk)	+	–	–	–	–
Bilateral occipital	Pulsating	Daily continuous (3 mo)	+	–	+	+	+
Unilateral L sided	Pulsating	Daily continuous (6 mo)	+	–	–	–	–
Bilateral occipital vertex	Pulsating	Daily continuous (1 y)	+	+	–	+	–
Unilateral R frontal	Pulsating	Daily continuous (3 d-wk)	+	+	–	–	+
Unilateral L orbital	Pulsating	Daily continuous (3 y)	+	+	–	–	–
Bilateral 5/10	Pulsating 8/10	Daily/continuous, 10/10	Nausea/ vomiting, 9/10	Phonophobia/ photophobia, 3/10	Aura, 2/10	Pulsatile tinnitus, 4/10	Vertigo/ dizziness, 5/10

*All 10 patients had headache in the morning. Plus sign indicates yes; minus sign, no; and numbers in virgule construction, number of 10 with the profile item.
†None had transient visual obscurations.

Table 4.—Headache Characteristics (Literature Review)*

	Source, y					
Characteristic	Lipton and Michelson,[10] 1972	Scanarini et al,[13] 1979	Spence et al,[14] 1980	Foley and Posner,[20] 1975	Wall,[26] 1990	Present Study
Headache present	1/1	1/1	9/9	1/4	58/63	10/10
Location						
Unilateral	0/1	. . .	0/6	0/1	31/58	5/10
Bilateral	1/1	. . .	6/6	1/1	27/58	5/10
Quality						
Pulsating	1/1	. . .	2/5	. . .	48/50	8/10
Pressure/ache	0/1	. . .	3/5	. . .	. . .	2/10
Severity, severe	1/1	1/1	5/6	1/1	54/58	10/10
Duration, continuous	. . .	. . .	6/7	. . .	43/58 > 1 h	10/10
Frequency, daily	1/1	. . .	6/7	. . .	43/58	10/10
Associated symptoms						
Nausea/vomiting	–	1/1	3/9	–	33/58	9/10
Photophobia/phonophobia	–	–	–	–	. . .	3/10
Tinnitus	–	–	–	–	35/58	4/10
Vertigo/Light-headedness	–	–	–	–	. . .	5/10

*Data are given as number of patients. Minus sign indicates none.

the patients had no characteristic fundus changes to suggest earlier papilledema. The chronic IIH postulate is supported by the chronicity of symptoms and the resemblance of our patients to those with classic IIH.

Intermittent elevation of intracranial pressure below the threshold needed to produce papilledema is another possibility. All but one of our patients had a persistent elevation of CSF pressure greater than 250 mm with serial LPs. The threshold pressure level needed to develop papilledema is unknown. We included a single case of a nonobese female with an opening pressure of 230 mm H$_2$O.

The mechanism of headache in increased intracranial pressure is unknown. Pseudotumor cerebri, high-pressure hydrocephalus, intracranial infections, hemorrhages, or neoplasms may produce headache and elevated intracranial pressure. However, as documented in patients with brain tumors, there can be headache without increased pressure. In a series of 72 patients, headache occurred as often in those without elevated intracranial pressure (19 of 23) as in those with increased pressure (46 of 49).[47] Traction on intracerebral pain-sensitive vessels, transient herniation of hippocampal gyri, and traction on cranial/cervical nerves with increased CSF pressure are postulated mechanisms of headache development. Alternately, changes in CSF pressure or flow may stimulate or inhibit central nervous system receptors (ie, adenosine receptors) that produce headache.

Treatment Modalities

The headache of patients with IIH and papilledema has frequently responded to standard headache treatment, including β-adrenergic blockers, calcium channel antagonists, antidepressant therapy, monoamine oxidase inhibitors, anticonvulsant therapy, analgesics, and ergotamine preparations. More aggressive surgical treatment of IIH has been directed toward preventing visual loss secondary to papilledema.

Table 5.—Demographics and Historical Findings*

Characteristic	Finding
Age range (average), y	26-46 (37.5)
Sex, F	8/10
No. of patients	
Hypertension	4/10
Menstrual irregularities (women)	6/8
Head trauma/meningitis/SAH	4/10
Failure of standard headache therapy	10/10

*SAH indicates subarachnoid hemorrhage.

Table 6.—Physical Examination*

	Finding	No. of Patients
General examination	WNL	10/10
Blood pressure	WNL	10/10
Neurologic examination	WNL	10/10
Weight	Obese (24%-100% >IBW)	8/10

*WNL indicates within normal limits; IBW, ideal body weight.

Once the diagnosis of increased intracranial pressure is made, secondary causes should be sought out and eliminated. More than 50 diseases, conditions, toxins, or pharmaceuticals have been associated with IIH.[15] Obese patients should be encouraged to lose weight.

As in patients with classic IIH, patients with elevated intracranial pressure without papilledema should have a trial of standard headache therapy that, in general, diminishes duration or severity of headache but does not prevent its recurrence. Treatment of patients with IIH without papilledema should include (1) elimination of symptomatic causes, (2) weight loss if the patient is obese, (3) standard headache treatment, (4) carbonic anhydrase inhibitors and loop diuretics, (5) short course of high-dose corticosteroids, (6) serial LPs, (7) lumboperitoneal or ventriculoperitoneal shunts, and (8) possibly optic nerve sheath fenestration. These types of treatment are detailed further.

If aggressive headache therapy is unsuccessful, then diuretics or a potent carbonic anhydrase inhibitor (acetazolamide) should be given in a 4- to 6-week trial. These drugs have decreased the frequency and severity of elevated intracranial pressure headache.[1,31]

The use of high-dose steroids (prednisone or dexamethasone) is controversial, but may be effective.[1,15] Rebound headache is common when steroids are withdrawn. Their prolonged use produces many adverse side effects. If started, steroid therapy should be limited to a strict, short, 2- to 4-week trial.

Lumbar puncture typically relieves headache in IIH.[1,5,10] We removed enough CSF to decrease the intracranial pressure to 100 to 150 mm of CSF. Although all patients had immediate relief, headaches recurred in several days to several months. Cerebrospinal fluid is rapidly replaced. Prolonged symptomatic relief may reflect a persistent CSF leak. Alternately, transient reduction of CSF pressure may allow decompression of the arachnoid villi, allowing for prolonged enhanced CSF absorption. A repeated LP temporarily controls the headache of increased intracranial pressure. However, its long-term usefulness is controversial.

A patient with severe incapacitating headache that does not respond to medical therapy or repeated LPs may need surgical management. Subtemporal decompression, lumboperitoneal shunt, ventriculoperitoneal shunt, and optic nerve sheath fenestration have been used to treat patients with IIH and papilledema.[12,14,31,32,48-54] Subtemporal decompression is complicated by seizure and stroke, and it has largely been replaced with shunting procedures. In the report of IIH without papilledema by Spence et al,[14] six of nine of their pa-

Table 7.—Ophthalmoscopic Examination*

		No. of Patients
Fundi	WNL	9/10 (drusen, 1)
	Papilledema	0/10
	Venous pulsations	8/9
Visual fields	WNL	9/10
	Bilateral superior temporal field cut	1/10
Visual acuity	WNL	19/20 eyes
	Light perception	1/20 eyes
Fluorescein angiogram	WNL	7/7

*WNL indicates within normal limits.

Table 8.—Investigations*

Study			No. of Patients
LP			
	Elevated Opening pressure, mm H_2O	Range, 230-450; average, 322	**10/10**
	Composition	WNL	7/10
		Low protein content	3/10
MRI/CT		WNL	6/10
		Empty sella	2/10
		Small ventricles	1/10
		Cortical atrophy	1/10

*LP indicates lumbar puncture; WNL, within normal limits; MRI, magnetic resonance imaging; and CT, computed tomography.

Table 9.—Headache Profile

Headache Characteristic	No. of Patients
Frequency	
Daily/continuous	10/10
Location	
Bilateral	5/10 (ventral, frontal, occipital)
Unilateral	5/10 (R or L frontal, orbital)
Quality	
Pulsating	8/10
Aching	2/10
Severity	
Severe	10/10
Present on awakening	10/10
Associated symptoms	
Nausea/vomiting	9/10
Phonophobia/photophobia	3/10
Aura	2/10
Pulsatile tinnitus	4/10
Vertigo/dizziness	5/10
Transient visual obscuration	0/10

Table 10.—Reasons for LP*

Reason	No. of Patients	
Rule out SAH	3/10	4/10
Rule out SAH and failure of medical therapy	1/10	
Rule out meningitis	2/10	4/10
Rule out meningitis and refractory headache	2/10	
Rule out pseudotumor cerebri	1/10	
Refractory headache/fits profile of pseudotumor	1/10	
Total	**10/10**	

*LP indicates lumbar puncture; SAH, subarachnoid hemorrhage.

tients were treated successfully with a lumboperitoneal shunt. Shunting procedures resolved elevated intracranial pressure headache in three of our patients; two patients had ventriculoperitoneal shunts, and the other patient had a lumboperitoneal shunt. Our three patients who required shunting procedures were severely incapacitated and unable to function before surgery. Two of these patients had postoperative LPs that showed normal CSF pressure at a time when they were free of headaches, and all three patients had significant improvement in their headaches.

Optic nerve sheath fenestration entails surgical incision of the dura mater that covers the optic nerve. The proposed mechanism in patients with IIH involves decompression of the optic nerve and continuous CSF drainage. In patients with papilledema and headache treated with optic nerve sheath fenestration, Corbett and coworkers[32] showed 65% efficacy in relieving medically uncontrolled headache. In 1988, Sergott and colleagues,[52] with the use of a modified optic nerve sheath decompression procedure, relieved headache in 13 of 17 patients with IIH. Optic nerve sheath fenestration has been performed on patients with unilateral papilledema but, to our knowledge, not on those patients with IIH without papilledema.

Follow-up

Patients with IIH without papilledema should undergo periodic neurologic follow-up. The neurologist should lower the intracranial pressure, control the headache, document changes in neurologic examination results, and encourage weight loss. The neurologist also should look for papilledema at every visit, since persistently elevated CSF pressure may predispose these patients to the development of papilledema and visual loss.

Neurologists, internists, and ophthalmologists who are faced with cases of severe, persistent headache with normal ophthalmoscopic examination results and normal findings from neuroimaging studies should rule out increased intracranial pressure.

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References

1. Weisberg LA. Benign intracranial hypertension. *Medicine (Baltimore)*. 1975;54:197-207.

2. Repka MX, Savino PJ. Pseudotumor cerebri. *Am J Ophthalmol*. 1984;98:741-746.

3. Ahlskog JE, O'Neill BJ. Pseudotumor cerebri. *Ann Intern Med*. 1982;97:249-256.

4. Johnston I, Paterson A. Benign intracranial hypertension, diagnosis and prognosis. *Brain*. 1974;97:289-300.

5. Paterson R, Depasquale N, Mann S. Pseudotumor cerebri. *Medicine (Baltimore)*. 1961;40:85-99.

6. Foley J. Benign forms of intracranial hypertension—'toxic' and 'otitic' hydrocephalus. *Brain*. 1955;78:1-41.

7. Berg L, Rosomoff HL, Aronson N, Silberman M, Pool JL. The syndrome of increased intracranial pressure without localizing signs. *Arch Neurol Psychiatry*. 1955;74:498.

8. Langiftt TW. Increased intracranial pressure. *Clin Neurosurg*. 1969;16:436-468.

9. Quincke H. Uber Meningitis Serosa and verwandte Zustande. *Dtsch Z Nernenheilkd*. 1897;9:149.

10. Lipton HL, Michelson PE. Pseudotumor cerebri syndrome without papilledema. *JAMA*. 1972;220:1591-1592.

11. Sher NA, Wirtschaffer J, Shapiro SK, See C, Shapiro I. Unilateral papilledema in 'benign' intracranial hypertension (pseudotumor cerebri). *JAMA*. 1983;250:2346-2347.

12. Maxner CE, Freedman MI, Corbett JJ. Asymmetric papilledema and visual loss in pseudotumor cerebri. *Can J Neurol Sci*. 1987;14:593-596.

13. Scanarini M, Mingrino S, d'Avella D, Della-Cort V. Benign intracranial hypertension without papilledema: a case report. *Neurosurgery*. 1979;5:376-377.

14. Spence JD, Amacher AL, Willis NR. Benign intracranial hypertension without papilledema: role of 24 hour cerebrospinal fluid pressure monitoring in diagnosis and management. *Neurosurgery*. 1980;7:326-336.

15. Corbett JJ. Diagnosis and management of idiopathic intracranial hypertension (pseudotumor cerebri). In: Shults WT, ed. *Focal Points 1989: Clinical Modules for Ophthalmologists*. San Francisco, Calif: American Academy of Ophthalmology; 1989;7(module 3):1-12.

16. Andres R. Mortality and obesity: the rationale for age-specific height-weight tables: Metropolitan Life Insurance Company–age specific recommendations. In: Andres R, Hazzard WR, Birman E, eds. *Principles of Geriatric Medicine*. New York, NY: McGraw-Hill International Book Co; 1985:1070.

17. Durcan FJ, Corbett JJ, Wall M. The incidence of pseudotumor cerebri: population studies in Iowa and Louisiana. *Arch Neurol*. 1988;45:875-877.

18. Digre KB, Corbett JJ. Pseudotumor cerebri in men. *Arch Neurol*. 1988;45:866-872.

19. Greer M. Benign intracranial hypertension, VI: obesity. *Neurology*. 1965;15:382-388.

20. Foley KM, Posner JB. Does pseudotumor cerebri cause the empty sella syndrome? *Neurology*. 1975;25:565-569.

21. Donaldson JO, Binstock ML. Pseudotumor cerebri in an obese woman with Turner syndrome. *Neurology*. 1981;31:758-760.

22. Donaldson JO. Endocrinology of pseudotumor cerebri. *Neurol Clin*. 1986;4:919-927.

23. Giuseffi V, Wall M, Siegal PZ, Rojas PB. Symptoms and disease associations in idiopathic intracranial hypertension (pseudotumor cerebri): a case-control study. *Neurology*. 1991;41:239-244.

24. Sismanis A. Otologic manifestations of benign intracranial hypertension syndrome: diagnosis and management. *Laryngoscope*. 1987;97:1-17.

25. Wall M, George D. Idiopathic intracranial hypertension: a prospective study of 50 patients. *Brain*. 1991;114:155-180.

26. Wall M. The headache profile of idiopathic intracranial hypertension. *Cephalalgia*. 1990;10:331-335.

27. Foley KM. Is benign intracranial hypertension a chronic disease? *Neurology*. 1977;27:388.

28. Walsh TJ, Garden JW, Gallagher B. Obliteration of retinal venous pulsations. *Am J Ophthalmol*. 1969;67:954-956.

29. Corbett JJ, Savino PJ, Thompson HS, et al. Visual loss in pseudotumor cerebri: follow-up of 57 patients from five to 41 years and a profile of 14 patients with permanent severe visual loss. *Arch Neurol*. 1982;39:461-474.

30. Corbett JJ, Jacobson DM, Mauer RC, Thompson HS. Enlargement of the blind spot caused by papilledema. *Am J Ophthalmol*. 1988;105:261-265.

31. Corbett JJ, Thompson HS. The rational management of idiopathic intracranial hypertension. *Arch Neurol*. 1989;46:1049-1051.

32. Corbett J, Nerad JA, Tse DT, Anderson RL. Results of optic nerve sheath fenestration for pseudotumor cerebri: the lateral orbitotomy approach. *Arch Ophthalmol*. 1988;106:1391-1397.

33. Bjerre P, Lindholm J, Gyldensted C. Pseudotumor cerebri: a theory on etiology and pathogenesis. *Acta Neurol Scand*. 1982;66:472-481.

34. Fishman RA. The pathophysiology of pseudotumor cerebri: an unsolved puzzle. *Neurology*. 1984;41:257-258.

35. Donaldson JO. Pathogenesis of pseudotumor cerebri syndromes. *Neurology*. 1981;31:877-880.

36. Janny P, Chazal J, Colnet G, Irthom B, Georget AM. Benign intracranial hypertension and disorders of CSF absorption. *Surg Neurol*. 1981;15:168-174.

37. Gjerris F, Sorenson S, Vorstrup S, Paulson OB. Intracranial pressure, conductance to cerebrospinal fluid outflow, and cerebral blood flow in patients with benign intracranial hypertension (pseudotumor cerebri). *Ann Neurol*. 1985;17:158-162.

38. Borgesen SE, Gjerris F. Relationships between intracranial pressure, ventricular size, and resistance to CSF outflow. *J Neurosurg*. 1987;67:535-539.

39. Johnston I. Reduced CSF absorption syndrome: reappraisal of benign intracranial hypertension and related conditions. *Lancet*. 1973;2:418-421.

40. Fishman RA. Pathophysiology of pseudotumor. *Ann Neurol*. 1979;5:496.

41. VanAlphen HAM. Migraine, a result of increased CSF pressure: a new pathophysiologic concept (preliminary report). *Neurosurg Rev*. 1986;9:121-124.

42. Vassilouthis J, Uttley D. Benign intracranial hypertension: clinical features and diagnosis using computed tomography and treatment. *Surg Neurol*. 1979;12:389-392.

43. Silbergleit R, Jonck L, Gebarski SS, Hatfielkd MK. Idiopathic intracranial hypertension (pseudotumor cerebri): MR imaging. *Radiology*. 1989;170:207-209.

44. George AE. Idiopathic intracranial hypertension: pathogenesis and the role of MR imaging. *Radiology*. 1989;170:21-22.

45. Weisberg LA. Computed tomography in benign intracranial hypertension. *Neurology*. 1985;35:175-178.

46. Corbett JJ, Mehta MP. Cerebrospinal fluid pressure in normal obese subjects and patients with pseudotumor cerebri. *Neurology*. 1983;33:1386-1388.

47. Alksne JF. Headache and brain tumor. In: Dalessio DJ, ed. *Wolff's Headache and Other Head Pain*. 4th ed. New York, NY: Oxford University Press; 1980:287-300.

48. Sorensen PS, Krogsaa B, Gjerris F. Clinical course and prognosis of pseudotumor cerebri: a prospective study of 24 patients. *Acta Neurol Scand*. 1988;77:164-172.

49. Johnston I, Besser M, Morgan MK. Cerebrospinal fluid diversion in the treatment of benign intracranial hypertension. *J Neurosurg*. 1988;69:195-202.

50. Gutgold-Glen H, Kattah JC, Chavis RM. Reversible visual loss in pseudotumor cerebri. *Arch Ophthalmol*. 1984;102:403-406.

51. VanderArk GD, Kempe LH, Smith DR. Pseudotumor cerebri treated. *JAMA*. 1971;217:1832-1834.

52. Sergott RC, Savino PJ, Bosley TM. Modified optic nerve sheath decompression provides long-term visual improvement for pseudotumor cerebri. *Arch Ophthalmol*. 1988;106:1384-1390.

53. Tse DT, Nerad JA, Anderson RL, Corbett JJ. Optic nerve sheath fenestration in pseudotumor cerebri: a lateral orbitotomy approach. *Arch Ophthalmol*. 1988;106:1458-1462.

54. Brourman ND, Spoor TC, Ramocki JM. Optic nerve sheath decompression for pseudotumor. *Arch Ophthalmol*. 1988;106:1378-1383.

Tuberous Sclerosis Complex in Olmsted County, Minnesota, 1950-1989

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• The incidence of tuberous sclerosis complex in Olmsted County, Minnesota, was 0.28 per 100 000 person-years from 1950 through 1989, the point prevalence on December 31, 1989, was 6.9 per 100 000 persons, and the incidence at birth was 6.0 per 100 000 live births. The incidence was 0.13 per 100 000 person-years from 1950 through 1974 and 0.46 per 100 000 person-years from 1975 through 1989. The higher rate of diagnosis during the later period is believed to be due to the use of computed tomography. Of the 12 patients considered in this study, one patient presented with seizures and severe intellectual disability, six patients presented with seizures, three patients presented with multiple facial angiofibroma, and two patients were asymptomatic.

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Tuberous sclerosis complex (TSC) is an autosomal dominant condition characterized by the presence of hamartomas and hamartias in one or more organs. Nearly any organ in the body can be affected. In the past, it was diagnosed only when a patient had seizures, severe mental disability, and multiple facial angiofibroma. We now know that these clinical features are only the tip of the iceberg and that there is a great variety of phenotypes[1] depending on the organ or organs affected. Since the introduction of computed tomography (CT)[2] in 1973 and magnetic resonance imaging in 1982, it has been easier to detect subependymal nodules and cortical tubers, allowing earlier diagnosis of the cerebral involvement by TSC. Likewise, renal CT or ultrasonography may detect hamartomas and cysts. Detection of these features has led to delineation of the different phenotypes.

In a study of the population of Rochester, Minn, Wiederholt et al[3] found the incidence rate of TSC to be 0.56 per 100 000 person-years and the prevalence rate to be 10.6 per 100 000 persons. From a study of all patients with TSC seen at the Mayo Clinic, Rochester, Minn, the original study has been updated and expanded to ascertain the birth and total incidence rates for the period 1950 through 1989 and the prevalence rate on December 31, 1989, in Olmsted County, Minnesota.

PATIENTS AND METHODS

All Olmsted County patients with a diagnosis of TSC were identified from the central records of the Mayo Clinic and the Olmsted Medical Group, which provide almost all of the medical care for local residents.[4] Patients were selected according to published criteria[5] (Table).

In addition to a review of all cases diagnosed as TSC during the 40-year period, a search was made for other cases of TSC by reviewing the records of patients registered since 1982 who had a dismissal diagnosis in one of the following categories: benign retinal tumor, fibroma, benign renal tumor, polycystic kidney disease, adenoma sebaceum, myoclonic seizures, infantile spasms, angiofibroma, cerebral hamartoma, and benign cerebral astrocytoma. Review of 555 records in this group yielded no additional cases.

For inclusion in the incidence study, the patients had to be bona fide residents of Olmsted County at the time of diagnosis. Any patient who had moved to Rochester to facilitate diagnosis and treatment was excluded from the incidence and prevalence studies.

Point prevalence was determined on December 31, 1989. The incidence rate, which covered the period 1950 through 1989, and the prevalence rate were calculated by using the decennial census data for the denominator. The 95% confidence intervals (CI) were based on the Poisson distribution.[6] The incidence rates are presented for the 40-year period and also for 1950 through 1974 and 1975 through 1989 to evaluate changes that may have occurred due to the introduction of CT in 1973 as a method of early diagnosis.

RESULTS

Twelve patients were considered in both the prevalence and the incidence studies. Two patients who resided in Olmsted County on the prevalence date were excluded from the incidence study, because their illness was diagnosed before they became residents of the County.

Ten patients (six male and four female) were first diagnosed as having TSC while living in Olmsted County during the study period. The mean patients' age at diagnosis was 14.7 years (range, 2 months to 53 years). The age-adjusted incidence rates per 100 000 person-years in the Rochester population with 95% CI were as follows: 1950 through 1974, 0.13 (CI, −0.02, 0.28), three cases; 1975 through 1989, 0.46 (CI, 0.11, 0.80), seven cases; and 1950 through 1989, 0.28 (CI, 0.01, 0.45), 10 cases.

The seven patients (four male and three female) with TSC, residing in Olmsted County (population of 101 974) on December 31, 1989, represent a prevalence rate of 6.9 per 100 000 persons (CI, 2.8, 14.4). Of the 66 478 children born to Rochester residents during 1950 through 1989, four were later found to have TSC, for a birth incidence of 6.0 per 100 000 live births.

Two patients who had participated in the previous study were excluded from this study. One of them, a child with TSC and severe mental disability, had

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Criteria for Definitive Diagnosis of Tuberous Sclerosis*

Cortical tubers (on CT or MRI)
Subependymal glial nodules (on CT or MRI)
Retinal hamartomas
Facial angiofibromas
Ungual fibroma
Forehead or scalp fibrous plaque
Renal angiomyolipomas

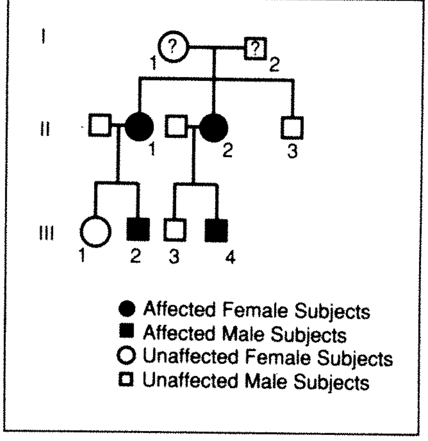
*CT indicates computed tomography; MRI, magnetic resonance imaging.

been a resident in the Rochester State Hospital, but her condition was diagnosed before she entered the County and she was no longer an Olmsted County resident. The other had a diagnosis based only on a facial angiofibroma, and a new review of the skin biopsy sections failed to confirm this diagnosis.

In a family (Figure) with members who had TSC, four members (I-1, I-2, II-1, and III-2) were Olmsted County residents on the prevalence date. Two other members of this family known to be affected (II-2 and III-4) did not live in this county when diagnosed. One of the parents (generation I) must have TSC, because two of their children have it. The parents are both in good health, have no obvious stigmata of the condition, and have never had seizures. The CT scan of patient II-2 shows calcified subependymal nodules; this patient had seizures as a child and has numerous hypomelanotic skin macules. Her son, III-4, has many hypopigmented skin macules and had infantile spasms and partial seizures later; a magnetic resonance imaging of his head showed subcortical areas of increased signal in T2 sequences, which suggests the presence of tubers.

Of the nine other patients considered in either the prevalence or the incidence study, one boy (who died) had severe intellectual disability and seizures. Four patients with seizures have an average intellectual ability. In one of these patients, the diagnosis was based on the presence of multiple facial angiofibromas; in three other patients, who presented with seizures, the diagnosis was made by CT. Computed tomography was also used to make the diagnosis in the father of one of these patients, a resident of Olmsted County. The three remaining patients presented with facial angiofibroma.

Five of the seven patients who presented in the 1975 through 1989 period were diagnosed by CT.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● Affected Female Subjects
■ Affected Male Subjects
○ Unaffected Female Subjects
□ Unaffected Male Subjects

Family pedigree of a family in Olmsted County, Minnesota, with members who had tuberous sclerosis complex.

COMMENT

The earliest studies to determine the frequency of TSC, done on patients in institutions for the mentally defective, suggested that the prevalence in the general population was about 1 per 100 000 persons.[7] Hunt and Lindenbaum[8] estimated the prevalence from source at 1:29 900 (3.3 per 100 000 persons) in the general population and at 1:15 400 (6.7 per 100 000 persons) among children under the age of 5 years. In an attempt at total ascertainment in the west of Scotland, Sampson et al[9] found a prevalence of 1:26 500 (3.8 per 100 000 persons) in the population and 1:12 000 (8.3 per 100 000 persons) for children under the age of 12 years. Point prevalence of TSC in our study, 6.9 per 100 000 persons, is very close to the results found in other populations. It is lower than the previous estimate for Rochester, 10.6 per 100 000 persons, but this difference is due to the exclusion of two of the patients included in the previous study.[3]

For the same reason, the overall incidence rate is lower in this study than in the previous one. Although based on a small number of cases and, therefore, very unstable, the incidence rate is higher in the more recent period. This may be due, in part, to the use of CT scan which allows an early diagnosis of TSC by detecting the subependymal nodules, and also reflects a better understanding of the nature of the disease, which led to the diagnosis in two asymptomatic cases. Magnetic resonance imaging helped to make the diagnosis in patient III-2, and it may be a useful way of detecting asymptomatic persons with TSC.

The birth incidence of 1:16 619 is lower, but not significantly, than is the prevalence rate in the general population of Olmsted County. It is possible that some affected persons who were born in Olmsted County had moved from the community prior to diagnosis of TSC. The diagnosis of TSC may be made in young children who present with infantile spasms[10] or other type of seizure, but the diagnosis may not be made until adulthood if the presenting symptom is not seizures but is the result of renal, pulmonary, or other pathologic conditions. It is clear that, in the present state of knowledge, birth incidence as determined in this study is not the best method of estimating the true incidence of TSC.

Of the 12 patients in our study, one patient had an intellectual disability and seven patients had seizures. In the larger study of all patients seen with TSC at Mayo Clinic and which, therefore, is influenced by referral bias, 48% had intellectual impairment and 78% had seizures.[11]

Because of small numbers, the Olmsted County study may not reflect accurately the number of patients that one would expect to find with an intellectual disability due to TSC, whereas the estimate of seizure prevalence in patients with TSC based on this study is more accurate. The small number of patients does not allow accurate estimation of the frequency of other pathologic conditions that are described in TSC. However, it does demonstrate that some cases of TSC are asymptomatic. Future population-based studies of TSC should include investigation of members of the families of those known to have TSC to provide a better estimate of disease frequency.

References

1. Gomez MR. Varieties of expression of tuberous sclerosis. *Neurofibromatosis.* 1988;1:330-338.
2. Konishi Y, Ito M, Okuno T, et al. Tuberous sclerosis: early neurologic manifestations and CT features in 18 patients. *Brain Dev.* 1979;1:31-37.
3. Wiederholt WC, Gomez MR, Kurland LT. Incidence and prevalence of tuberous sclerosis in Rochester, Minnesota, 1950 through 1982. *Neurology.* 1985;35:600-603.
4. Kurland LT, Molgaard CA. The patient record in epidemiology. *Sci Am.* 1981;245:54-63.
5. Gomez MR. Criteria for diagnosis. In: Gomez MR, ed. *Tuberous Sclerosis.* 2nd ed. New York, NY: Raven Press; 1988:9-19.
6. Beyer WH, ed. *CRC Handbook of Tables for Probability and Statistics.* Cleveland, Ohio: Chemical Rubber Company; 1966:58-64.
7. Gunther M, Penrose LS. The genetics of epiloia. *J Genet.* 1935;31:413-430.
8. Hunt A, Lindenbaum RH. Tuberous sclerosis: a new estimate of prevalence within the Oxford region. *J Med Genet.* 1984;21:272-277.
9. Sampson JR, Scahill SJ, Stephenson JBP, Mann L, Connor JM. Genetic aspects of tuberous sclerosis in the west of Scotland. *J Med Genet.* 1989;26:28-31.
10. Pampiglione G, Pugh E. Infantile spasms and subsequent appearance of tuberous sclerosis syndrome. *Lancet.* 1975;2:1046.
11. Gomez MR. Neurologic and psychiatric features. In: Gomez MR, ed. *Tuberous Sclerosis.* 2nd ed. New York, NY: Raven Press; 1988:21-36.

Standard and Controlled-Release Levodopa/Carbidopa in Patients With Fluctuating Parkinson's Disease on a Protein Redistribution Diet

A Preliminary Report

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• Ten patients with Parkinson's disease (PD) with motor fluctuations that responded to a protein redistribution diet were studied. All 10 patients were receiving standard Sinemet (levodopa/carbidopa). Five randomly selected patients were changed from standard Sinemet to a controlled-release form of Sinemet. The other five patients continued to receive standard Sinemet. To maintain the same degree of control of PD in the five patients switched to the controlled-release form of Sinemet, the daily levodopa intake increased. While receiving optimal therapy (standard Sinemet or controlled-release Sinemet) and a protein redistribution diet, all 10 patients then underwent hourly videotaping and blood sampling (for plasma levodopa levels) during 2 consecutive days. Videotapes were blindly reviewed for PD disability, dyskinesia, and the time required to walk a measured distance. Comparing the two groups, standard Sinemet with controlled-release Sinemet, respectively, mean levodopa requirements were 505 and 1895 mg, plasma levodopa levels were 6.1 and 17.6 μmol/L, and abnormal involuntary movement scale scores were 14 and 26. Their mean PD disability scores did not differ statistically or clinically. Also no statistically significant differences were noted in either their mean walking times or their mean daily dose frequencies.

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Motor fluctuations and unpredictable periods of levodopa unresponsiveness associated with dopamine replacement therapy can be difficult to control and are a major problem in the long-term management of advanced Parkinson's disease (PD).[1-6] Pharmacokinetic factors play a significant role in the deterioration of efficacy of levodopa.[3] To reach the central nervous system, plasma levodopa must cross the blood-brain barrier by a carrier-mediated mechanism. Large neutral amino acids compete with levodopa for this carrier. By simply eliminating daytime protein with a protein redistribution diet (PRD), sensitivity to levodopa (standard Sinemet) in many patients with fluctuating PD can be restored.[7-17]

Patients with severe PD can have depletion of more than 95% of brain dopamine stores.[18] In such cases, successful replacement therapy would, therefore, depend on the constant and continuous availability of levodopa. Several studies have reported that fluctuations can be eliminated by using continuous intravenous[3,19-22] and intraintestinal[23,24] levodopa infusions. The development of controlled-release dopaminergic preparations for oral administration has been encouraged by this successful, though usually impractical, use of continuous levodopa infusions.

One controlled-release form of Sinemet (Sinemet CR4, Merck & Co Inc, West Point, Pa) contains 50 mg of carbidopa and 200 mg of levodopa and is formulated in a slow-eroding matrix to allow for the gradual release of its contents. This formulation is designed to permit a more prolonged absorption of both ingredients resulting in the elimination of the sharp plasma levodopa peaks associated with standard Sinemet, while yielding higher end-of-dose plasma levels during long-term therapy.[25] Thus, peak antiparkinsonian effect is expected to occur later and last longer with the controlled-release preparation.[26] It may be most effectively used by patients requiring frequent dosing among whom are many with motor fluctuations.

Results from the use of this trial preparation are encouraging, but controlled-

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released Sinemet has not been systematically compared with standard Sinemet in patients who are receiving a PRD. This preliminary report contrasts the effectiveness of these preparations in 10 patients receiving optimal therapy and a PRD. Optimal therapy was considered to be that dose and frequency of dose of drug (standard Sinemet or controlled-release Sinemet) that provided maximal relief of parkinsonian symptoms.

PATIENTS AND METHODS

Ten patients with moderate PD (Hoehn and Yahr stages 3 and 4), mean age of 64.7 years (range, 45 to 74 years), mean duration of disease of 10.7 years (range, 2 to 29 years), and mean duration of motor fluctuations of 3.4 years (range, 6 months to 9 years) that responded to and have been maintained on a PRD for a mean duration of 13.4 months (range, 5 to 24 months) were studied. All the patients were receiving optimal standard Sinemet therapy at the outset. To obtain optimal control of symptoms, four of the 10 patients were receiving adjuvant anti-PD therapy. These four patients did not differ from the other patients with repect to age at onset of PD, duration or severity of disease, or total daily dose and frequency of dose of levodopa. Their adjuvant therapy was unchanged during the course of the study.

Baseline outpatient clinical assessments (one per patient) were obtained on all patients. These included a PD disability score using the New York University (NYU) Disability Scale,[27] a dyskinesia score using the Abnormal Involuntary Movement Scale (AIMS),[28] and the time (in seconds) required to walk a measured distance, turn 180°, and return to the starting point.

Five patients, randomly selected, continued to receive standard Sinemet therapy (group 1) and the remaining five were changed to a regimen of controlled-release Sinemet therapy (group 2). No statistically significant differences were noted in age (65.8 and 63.6 years), duration of disease (14.6 and 10.6 years), NYU disability score (26.0 and 22.6), walking time (9 and 11 seconds), duration of fluctuations (4.1 and 2.7 years), or duration on the PRD (10.2 and 16.6 months) between the two groups (group 1 and group 2, respectively) at baseline. However, prior to being switched to controlled-release Sinemet, group 2 required a mean total standard Sinemet dose of 1165 mg, which was significantly greater ($P<.05$) than that required by group 1 (505 mg). Group 2 also required more daily standard Sinemet doses than group 1 (11.2 as compared with 6.0), although this difference was not statistically significant. In addition, three of the four patients maintained on a regimen of adjuvant therapy were randomized to group 1 and the fourth was randomized to group 2.

Once the controlled-release Sinemet dose and dosing frequency in the group 2 patients were optimized, a process that took 7 to 15 months (mean±SD, 11.4±3.6 months), a second outpatient clinical assessment was made of each of these five patients. The clinical scores, dose of levodopa, and frequency of levodopa administration obtained on these five group 2 patients when they were receiving optimal standard Sinemet therapy were compared with the corresponding values obtained when they were switched to optimal controlled-release Sinemet therapy using the paired *t* test (Table 1).

Table 1.—Patients With Fluctuating PD on PRD: Comparison Between Standard Sinemet and Controlled-Release Sinemet in Five Patients Switched From Standard Sinemet to Controlled-Release Sinemet (Group 2) (Dosage Adjusted to Produce Optimal NYU Disability Score)*

Factor†	Standard Sinemet	Controlled-Release Sinemet	Paired *t* Test
NYU score‡	10.4 ± 3.1	14.4 ± 5.1	NS
AIMS score‡	8.3 ± 4.1	26.2 ± 5.1	$P<.05$
Walking time, s‡	12.8 ± 2.9	10.6 ± 2.5	NS
Total levodopa dose, mg/24 h	1165 ± 224	1895 ± 491	NS
Total levodopa dose, mg/24 h (n = 4)§	1356 ± 151	2294 ± 371	$P<.05$
No. of levodopa doses per 24 h	11.2 ± 2.7	7.6 ± 1.2	NS
No. of levodopa doses per 24 h (n = 4)§	13 ± 2.6	8.8 ± 0.5	NS

*PD indicates Parkinson's disease; PRD, protein redistribution diet; NYU, New York University; AIMS, abnormal involuntary movement scale; and NS, not significant.

†Values are means ± SE.

‡Represents one data point per patient.

§Excluding the patient who had a reduction in levodopa dose when changed from standard Sinemet to controlled-release Sinemet.

Table 2.—Ten Patients With Fluctuating PD on PRD: Five Receiving Standard Sinemet and Five Receiving Controlled-Release Sinemet (Dosage Adjusted to Produce Optimal NYU Disability Score)*

Factor†	Standard Sinemet (Group 1)	Controlled-Release Sinemet (Group 2)	Student's *t* Test
NYU score‡	22.6 ± 1.5	22.2 ± 1.0	NS
AIMS score‡	14.0 ± 1.7	26.0 ± 1.8	$P<.05$
Walking time, s‡	17.2 ± 2.8	13.1 ± 0.4	NS
Total levodopa dose, mg/24 h	505 ± 69	1895 ± 491	$P<.05$
No. of levodopa doses per 24 h	6.0 ± 0.5	7.6 ± 1.2	NS
Plasma levodopa level, µmol/L‡	6.1 ± 0.8	17.6 ± 3.4	$P<.01$
Hours "on"/8 h	5.6 ± 0.8	6.6 ± 0.7	NS

*PD indicates Parkinson's disease; PRD, protein redistribution diet; NYU, New York University; AIMS, abnormal involuntary movement scale; and NS, not significant.

†Values are mean ± SE.

‡Represents eight data points per day, per patient, over a 2-day period.

The two groups were then further studied. All 10 patients (five receiving standard Sinemet and five receiving controlled-release Sinemet) underwent hourly videotaping of a standardized motor examination and blood sampling (for plasma levodopaa levels) from 9 AM to 4 PM on 2 consecutive days. Videotapes were separately reviewed and scored by a masked observer using the NYU scale, the AIMS, and the time (in seconds) to walk a measured distance. The number of "on" hours was also estimated from the videotapes. On time was regarded as that period that the patient was normal or mildly dyskinetic as opposed to "off" time in which the patient demonstrated signs of parkinsonism (ie, immobility, rigidity, and/or tremor). Scores obtained by patients in the two groups (standard Sinemet and controlled-release Sinemet) were compared using the Student's *t* test. Total daily levodopa dose and number of doses required by each group were also compared (Table 2).

One patient from group 2 then underwent hourly videotaping and blood sampling, from 10 AM to 4 PM as previously outlined, while receiving optimal controlled-release Sinemet therapy 1 day and then, after being restarted on a regimen of standard Sinemet, receiving optimal standard Sinemet therapy 3 days later. Scores obtained on each day were compared using the paired *t* test (Table 3).

RESULTS

To maintain the same degree of control of PD in the five patients changed from standard Sinemet to controlled-release Sinemet therapy, the mean daily levodopa intake increased significantly in four patients from 1356 to 2294 mg ($P<.05$) and decreased in the fifth patient from 400 to 300 mg while receiving standard Sinemet and controlled-release Sinemet therapy, respectively (Table 1). Overall, the mean daily dose increased from 1165 to 1895 mg, but this was not statistically significant (Table 1). The mean number of daily doses, comparing the five patients switched from standard Sinemet to controlled-release Sinemet therapy were 11.2 with standard Sinemet and 7.6 with controlled-release Sinemet (not statistically different).

Comparing the two groups, standard Sinemet with controlled-release Sinemet, respectively (Table 2), mean levodopa requirements were 505 and 1895 mg ($P<.05$). Plasma levodopa levels were 6.1 and 17.6 μmol/L ($P<.01$), AIMS scores were 14.0 and 26.0 ($P<.05$), and walking times were 17.2 seconds and 13.1 seconds (not significant). The PD disability scores were 22.6 and 22.2, respectively (not significant). Also no significant difference was noted in the daily dose frequency (6.0 and 7.6, respectively) or number of on hours per 8 hours of testing (5.6 and 6.6, respectively) between the two groups.

The results of the videotaping and blood sampling of the one patient from group 2 who was restarted on a regimen of standard Sinemet therapy are shown in the Figure. The total daily levodopa dose required by this patient dropped from 2800 (with controlled-release Sinemet) to 1600 mg (with standard Sinemet), total daily doses increased from eight (with controlled-release Sinemet) to 13 (with standard Sinemet), and mean plasma levodopa level dropped from 18.6 (with controlled-release Sinemet) to 8.4 μmol/L (with standard Sinemet). The patient's average PD disability score, dyskinesia score, and walking time were similar on the 2 days of testing (Table 3).

COMMENT

The much higher doses of levodopa necessitated by the controlled-release form of Sinemet were consequent to the formatting of the pill that contains 50 mg of carbidopa and 200 mg of levodopa. Higher dopa intake resulted in higher dopa blood levels and more dyskinesia, although PD disability scores and walking times were not significantly improved beyond the levels provided by standard Sinemet.

Raising blood dopa levels from moderate to high has been reported to cause dyskinesia without improving PD symptoms.[29,30] Controlled-release Sinemet did not permit a statistically significant reduction in the frequency of dosing, although some reduction in frequency did occur.

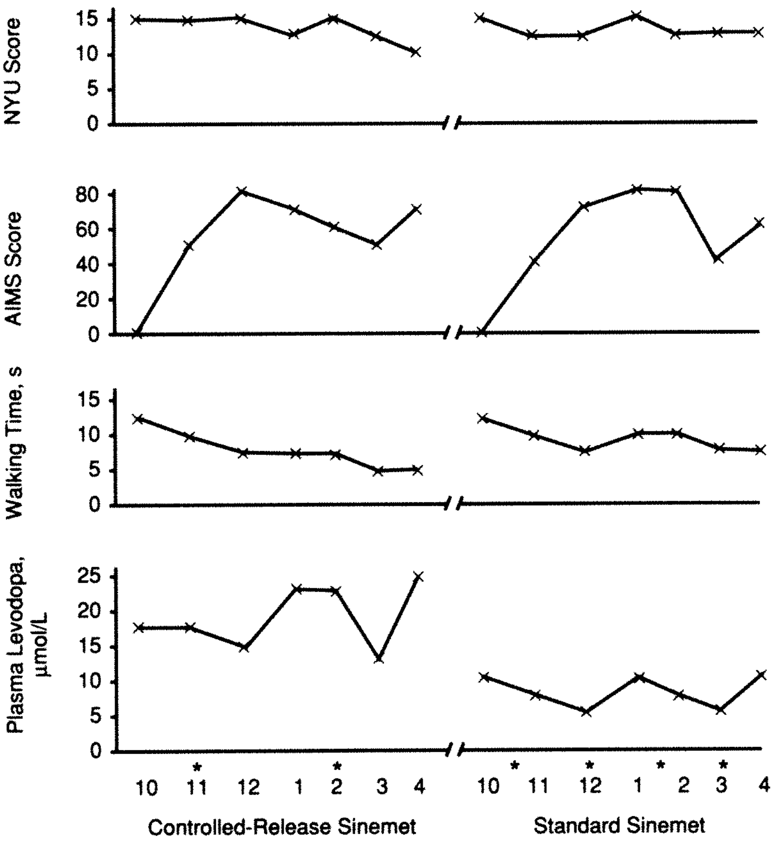
Table 3.—Comparison Between Controlled-Release Sinemet and Standard Sinemet in One Patient* Switched Back to Standard Sinemet From Controlled-Release Sinemet (Dosage Adjusted to Produce Optimal NYU Disability Score)†

Factor	Controlled-Release Sinemet	Standard Sinemet	Paired *t* Test
NYU score‡	13.0 ± 0.6	13.0 ± 0.3	NS
AIMS score‡	53.7 ± 9.8	51.6 ± 10.1	NS
Walking time, s‡	7.7 ± 0.8	8.9 ± 0.8	NS
Hours "on"/7 h	6	6	. . .
Total levodopa dose, mg/24 h	2800	1600	. . .
No. of levodopa doses per 24 h	8	13	. . .
Plasma levodopa level, μmol/L‡	18.6 ± 1.7	8.4 ± 0.8	$P<.01$

*The one patient from group 2 who was restarted on a regimen of standard Sinemet.

†NYU indicates New York University; AIMS, abnormal involuntary movement scale; and NS, not significant.

‡Represents seven data points over a 1-day period. Values are mean ± SE.



Analysis of response of patient receiving controlled-release Sinemet and then receiving standard Sinemet therapy. X axis indicates time of day (from 10 AM to 4 PM); asterisk, time of administration of Sinemet (standard or controlled release); NYU, New York University; and AIMS, abnormal involuntary movement scale.

The main reasons for using controlled-release Sinemet, as opposed to standard Sinemet, in patients with fluctuating PD would be to lower the dose frequency requirements and to increase on time while decreasing off time. In this regard, according to these preliminary data, controlled-release Sinemet was not particularly effective.

Although the patients were randomly allocated to treatment group, the small sample size resulted in a disparity in the baseline standard Sinemet requirements between group 1 and group 2. This may indicate that those patients in group 2 had more severe PD than their group 1 counterparts. However, no statistically significant differences were noted between the groups at baseline in age, duration of disease, NYU disability score, walking time, duration of motor fluctuations, or duration on the PRD. Furthermore, the additional data obtained on the one patient from group 2 who was restarted on a regimen of standard Sinemet therapy and then reassessed serves to support our preliminary conclusions.

Others have found some effectiveness of controlled-release Sinemet[31-36] in patients with fluctuating PD but did not simultaneously use the PRD. As the diet facilitates the central uptake of levodopa per se, its influence on both forms of Sinemet (standard and controlled release) would be the same, irrespective of their peripheral pharmacokinetic properties. However, the resultant improvement in the efficacy of standard Sinemet therapy is so dramatic[7-17] that, under conditions of daytime restriction of protein, treatment with controlled-release Sinemet does not seem to confer any further advantage. Further intrapatient trials of standard Sinemet and controlled-release Sinemet therapy, in conjunction with the PRD, involving larger numbers of patients will help to clarify the role of controlled-release Sinemet in patients who require the PRD.

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References

1. Marsden CD, Parkes JD, Quinn N. Fluctuations of disability in Parkinson's disease: clinical aspects. In: Marsden CD, Fahn S, eds. *Movement Disorders.* London, England: Butterworths; 1982: 96-122.
2. Fahn S. Fluctuations of disability in Parkinson's disease: pathophysiology. In: Marsden CD, Fahn S, eds. *Movement Disorders.* London, England: Butterworths; 1982:123-145.
3. Stocchi F, Ruggieri S, Brughitta G, Agnoli A. Problems in daily motor performances in Parkinson's disease: the continuous dopaminergic stimulation. *J Neural Transm.* 1986;22(suppl):209-218.
4. Crossman AR. A hypothesis on the pathophysiological mechanisms that underlie levodopa- or dopamine agonist-induced dyskinesia in Parkinson's disease: implications for future strategies in treatment. *Mov Disord.* 1990;5:100-108.
5. Granerus AK. Factors influencing the occurrence of 'on-off' symptoms during long-term treatment with L-dopa. *Acta Med Scand.* 1978;203: 75-85.
6. Rinne UK. Problems associated with long-term levodopa treatment of Parkinson's disease. *Acta Neurol Scand Suppl.* 1983;68:19-26.
7. Pincus JH, Barry K. Dietary method for reducing fluctuations in parkinsonism. *Yale J Biol Med.* 1987;60:133-139.
8. Pincus JH, Barry K. The influence of dietary protein upon motor fluctuations in Parkinson's disease. *Arch Neurol.* 1987;44:270-272.
9. Pincus JH, Barry K. Plasma levels of amino acids correlate with motor fluctuations in parkinsonism. *Arch Neurol.* 1987;44:1006-1009.
10. Pincus JH, Barry K. Protein redistribution diet restores motor function in patients with dopa-resistant off periods. *Neurology.* 1988;38:481-483.
11. Eriksson T, Granerus AK, Linde A, Carlsson A. 'On-off' phenomenon in Parkinson's disease: relationship between dopa and other large neutral amino acids in plasma. *Neurology.* 1988;38:1245-1248.
12. Kurlan R. Dietary therapy for motor fluctuations in Parkinson's disease. *Arch Neurol.* 1987;44:1119-1121.
13. Baruzzi A, Conti M, Riva R, et al. Influence of meal ingestion time on pharmacokinetics of orally administered levodopa in parkinsonian patients. *Clin Neuropharmacol.* 1987;10:527-537.
14. Riley D, Lang AE. Practical application of a low protein diet for Parkinson's disease. *Neurology.* 1988;38:1026-1031.
15. Carter JH, Nutt JG, Woodward WR, Hatcher L, Trotman T. Amount and distribution of dietary protein affects clinical response to levodopa. *Neurology.* 1989;39:552-556.
16. Tsui JKC, Ross S, Poulin K, et al. The effect of dietary protein on the efficacy of L-dopa: a double-blind study. *Neurology.* 1989;39:549-552.
17. Nutt JG, Woodward WR, Hammerstad JP, Carter JH, Anderson JL. The 'on-off' phenomenon in Parkinson's disease: relation to levodopa absorption and transport. *N Engl J Med.* 1984;310:483-488.
18. Hornykiewicz O. The mechanism of action of L-dopa in Parkinson's disease. *Life Sci.* 1974; 15:1249-1259.
19. Shoulson I, Glaubiger GA, Chase TN. On-off response: clinical and biochemical correlations during oral and intravenous levodopa administration in parkinsonian patients. *Neurology.* 1975;25:1144-1148.
20. Quinn N, Marsden CD, Parkes JD. Complicated response fluctuations in Parkinson's disease: response to intravenous infusion of levodopa. *Lancet.* 1982;2:214-215.
21. Quinn N, Marion MH, Stocchi F, Jenner P, Marsden CD. Intravenous dopamine agonist studies in Parkinson's disease. In: Fahn S, Marsden CD, Jenner P, eds. *Recent Developments in Parkinson's Disease.* New York, NY: Raven Press; 1986:247-253.
22. Chase TN, Baronti F, Fabbrini G, et al. Rationale for continuous dopaminomimetic therapy of Parkinson's disease. *Neurology.* 1989;39:7-10.
23. Stocchi F, Ruggieri S, Bravi D, Carta A, Agnoli A. Jejunal delivery of levodopa methylester in parkinsonism. *Neurology.* 1990;40(suppl 1):292.
24. Kurlan R, Nutt JG, Woodward WR, et al. Duodenal and gastric delivery of levodopa in parkinsonism. *Ann Neurol.* 1988;23:589-595.
25. Yeh KC, August TF, Bush DF, et al. Pharmacokinetics and bioavailability of Sinemet CR: a summary of human studies. *Neurology.* 1989;39: 25-38.
26. Cedarbaum JM, Kutt H, McDowell F. A pharmacokinetic and pharmacodynamic comparison of Sinemet CR (50/200) and standard Sinemet (25/100). *Neurology.* 1989;39:38-44.
27. Lieberman A. Parkinson's disease: a clinical review. *Am J Med Sci.* 1974;267:66-80.
28. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* Washington, DC: Psychopharmacology Research Branch; 1976:534-537. US Dept of Health, Education, and Welfare publication 76-338.
29. Rinne UK, Sonninen V, Siirtola T. Plasma concentration of levodopa in patients with Parkinson's disease. *Eur Neurol.* 1973;10:301-310.
30. Algeri S, Ruggieri S, Miranda F, Casacchia M, Morselli FL, Agnoli A. Absence of relationships between L-dopa plasma levels and therapeutic effect in Parkinson's disease. *Eur Neurol.* 1976;14:219-228.
31. Nutt TG, Woodward WR, Carter TH. Clinical and biochemical studies with controlled-release levodopa/carbidopa. *Neurology.* 1986;36:1206-1211.
32. Hutton JT, Morris JL, Román GC, Imke SC, Elias JW. Treatment of chronic Parkinson's disease with controlled-release carbidopa/levodopa. *Arch Neurol.* 1988;45:861-864.
33. Factor SA, Sanchez-Ramos JR, Weiner WJ, Ingenito AM. Efficacy of Sinemet CR4 in subgroups of patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1989;52:83-88.
34. Cedarbaum JM, Hoey M, McDowell FH. A double-blind crossover comparison of Sinemet CR4 and standard Sinemet in patients with Parkinson's disease and fluctuating motor performance. *J Neurol Neurosurg Psychiatry.* 1989;52:207-212.
35. Ahlskog JE, Muenter MD, McManis PG, Bell GN, Bailey PA. Controlled-release Sinemet (CR-4): a double-blind crossover study in patients with fluctuating Parkinson's disease. *Mayo Clin Proc.* 1988;63:876-886.
36. Cedarbaum JM, Breck L, Kutt H, McDowell FH. Controlled-release levodopa/carbidopa, II: Sinemet CR4 treatment of response fluctuations in Parkinson's disease. *Neurology.* 1987;37:1607-1612.

Pneumocystis carinii Pneumonia in Patients With Primary Brain Tumors

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• **All histologically documented episodes of *Pneumocystis carinii* pneumonia in adult patients with primary brain tumors treated at Memorial Sloan-Kettering Cancer Center, New York, NY, since 1981, were retrospectively reviewed. *Pneumocystis carinii* pneumonia was histologically documented 11 times in 10 patients. During the same 8-year interval, approximately 587 adults were seen at the center for a brain tumor, 90% of whom received ongoing therapy. Therefore, in at least 1.7% (10/587) of our patients with brain tumors, *P carinii* pneumonia developed. The median duration of dexamethasone therapy at the onset of *P carinii* pneumonia symptoms was 2.75 months. Symptoms began during tapering of steroid therapy in eight episodes. Bronchoscopy was diagnostic in the eight cases in which it was performed. Four episodes (40%) were fatal. Trimethoprim-sulfamethoxazole prophylaxis may be indicated in some patients with brain tumors, especially during tapering of steroid therapy.**

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Pneumocystis carinii is one of the most common opportunistic pathogens that causes pneumonitis in immunocompromised patients. There are a variety of predisposing immunodeficiency states, including hematologic malignant neoplasms.[1-5] In contrast, *P carinii* pneumonia (PCP) is rare in patients with solid tumors but may occur in these patients in the setting of corticosteroid therapy.[1,5-7] Patients with primary brain tumors often receive high doses of corticosteroids for prolonged periods, increasing the risk of opportunistic infections. To assess the magnitude of this problem in our patients with brain tumors, we reviewed all cases of PCP in patients with primary brain tumors treated at Memorial Sloan-Kettering Cancer Center (MSKCC), New York, NY. We determined the percentage of patients with brain tumors in whom PCP developed, the relationship of dexamethasone therapy to PCP, and the clinical features of PCP in this group of patients.

PATIENTS AND METHODS

The medical records of all adult patients treated at MSKCC since 1981 for a primary brain tumor and a histologically documented PCP diagnosis were reviewed. Cases were identified from the Memorial Hospital Data Analysis computerized database (containing diagnoses from clinic records of patients receiving their treatment at MSKCC, hospital discharge summaries, and autopsy reports) and from bronchoscopy records. To determine the size of the group at risk for PCP, we used the data analysis database to ascertain the total number of adults (aged ≥20 years) treated for a primary brain tumor from 1981 to 1989. Because pediatric patients with brain tumors at MSKCC are routinely treated with prophylactic trimethoprim-sulfamethoxazole during prolonged steroid therapy, we excluded all patients so treated from the group at risk by counting only patients who were at least 20 years old. To be certain that this database contained only patients who had ongoing therapy at MSKCC, 40 patients with a diagnosis of glioblastoma multiforme were selected from the group at risk for PCP and their records were reviewed for treatment and duration of follow-up.

In patients who underwent diagnostic bronchoscopy, bronchial washings and bronchoalveolar lavage were processed for bacterial, fungal, and mycobacterial staining and culture as previously described.[8] Cytologic examination was performed on bronchial brushings, washings, and lavage fluids using Papanicolaou and Gram-Weigert stains.[8] Gram-Weigert, Ziehl-Neelsen, and silver methenamine stains were performed on the transbronchial biopsy specimens in addition to the usual pathologic examination. All lung specimens were extensively examined and cultured, and their pathologic findings reviewed. *Pneumocystis carinii* pneumonia was diagnosed by the demonstration of cysts in bronchial fluid or lung tissue.

RESULTS

Patients With PCP

There were 11 histologically documented episodes of PCP in 10 patients with primary brain tumors between 1981 and 1989. The cases were distributed during this period as outlined in Table 1. Concurrently, 587 adult patients began treatment for a primary brain tumor at MSKCC. Approximately 90% of these 587 had follow-up adequate to identify episodes of PCP (see the following data). Therefore, during the last 8 years, PCP developed in at least 1.7% of our adult patients with brain tumors.

There were two patients with clinically suspected, but unconfirmed episodes, of PCP and two confirmed episodes in two patients with primary central nervous system lymphoma who were excluded from analysis. Of the remaining 10, six patients were men and four were women; their median age was 45 years; and all were white. The tumors were

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glioblastoma multiforme (five), anaplastic astrocytoma (three), brain-stem glioma (one), and medulloblastoma (episodes at the ages of 26 and 29 years occurred in this patient). The brain tumor was in the posterior fossa in six of the patients (medulloblastoma, brain-stem glioma, midbrain and thalamic glioblastoma, multifocal anaplastic astrocytoma, cerebellar anaplastic astrocytoma, and cervicomedullary junction anaplastic astrocytoma).

The interval from the time of tumor diagnosis to the time of diagnosis of PCP ranged from 3 weeks to 9 years, with a median of 3 months. Nine tumors were newly diagnosed and two were recurrent, one at 3 years and one at 8.5 years from the original tumor diagnosis. The patient with two episodes of PCP suffered the second episode during a recurrence 3 years following the original diagnosis.

All patients had received cranial irradiation. Single-agent or combination chemotherapy had been administered before the development of PCP in seven episodes (Table 1), including a nitrosourea (lomustine, PCNU [1-(2-chloroethyl)-3-(2,6 dioxo-3-piperadyl)-1-nitrosurea], or carmustine), procarbazine hydrochloride, vincristine sulfate, fluorouracil, hydroxyurea, mechlorethamine hydrochloride, and misonidazole. None of the five patients who received a nitrosourea had documented pulmonary toxic reaction from the agent. None of the patients had an identified human immunodeficiency virus risk factor other than one patient, who had had a blood transfusion between the first and second episodes of PCP. One patient had received trimethoprim-sulfamethoxazole for a urinary tract infection 3 months before the diagnosis of PCP.

All of the patients with PCP were receiving dexamethasone (Table 1). The duration of steroid therapy before the onset of PCP symptoms ranged from 5 weeks to 9.5 months (median, 2.75 months). The onset of symptoms in eight of the 11 episodes occurred while dexamethasone therapy was being tapered. The interval from the initiation of the tapering of steroid therapy to onset of PCP symptoms in these eight ranged from 1 to 63 days (median, 12 days). At the time of diagnosis of PCP, daily dexamethasone dose ranged from 2 to 60 mg.

Table 1.—Relationship of Steroid Therapy and Chemotherapy to PCP*

Episode (y)	Maximum Dosage of Dexamethesone, mg/d	Duration of Dexamethasone Therapy Before Symptoms of PCP, mo	Duration of Dexamethasone Taper Before Symptoms of PCP, d	Dexamethasone Dosage at Diagnosis of PCP, mg/d	Chemotherapy
1 (1982)	32	1.5	. . .†	8	Carmustine, hydroxyurea
2 (1982)	24	2.5	63	2	Lomustine, fluorouracil, misonidazole
3 (1983)	28	1.5	. . .†	20	None
4 (1983)	92	2.25	5	24	None
5 (1984)	24	9.5	21	12	PCNU
6 (1985)	32	3.0	17	12	Fluorouracil
7 (1986)	100	1.25	11	4	Mechlorethamine hydrochloride, vincristine
8 (1986)	24	3.25	1	8	Lomustine, vincristine, procarbazine
9 (1989)	48	3.25	14	32	None
10 (1989)	16	2.75	5	10	None
11 (1989)	96	4.25	. . .†	60	Carmustine

*PCP indicates *Pneumocystis carinii* pneumonia. Only those drugs in use at the time of the diagnosis of PCP are listed.

†Episodes occurring in the absence of a steroid taper.

Table 2.—Clinical Summary of 11 Episodes of PCP in Patients With Brain Tumors*

Episode	Symptoms	Duration of Symptoms Before PCP Diagnosis, d	(A-a)O_2 Gradient, mm Hg	LDH, U/L	Chest Roentgenography at First Evaluation of Symptoms	Outcome
1	NC, F	14	53	510	Bilateral infiltrates	Recovered
2	NC, D, F, CP	1	69	960	Bilateral infiltrates	Recovered
3	NC	14	73	672	Focal infiltrate	Recovered
4	PC, D, CP	1	51	336	Diffuse infiltrates	Recovered
5	D, F	7	215†	803	Bilateral infiltrates	Died
6	PC, D, F, CP	3	54	820	Focal infiltrate	Died
7	NC, D, F	30	. . .	1284	Diffuse infiltrates	Recovered
8	NC, D	22	35	419	Normal	Recovered
9	D	7	76	480	Diffuse infiltrates	Died
10	NC, CP	3	23.5	409	Bilateral infiltrates	Recovered
11	NC, D, F	10	. . .	499	Focal infiltrate	Died

*PCP indicates *Pneumocystis carinii* pneumonia; (A-a)O_2, alveolar-arterial oxygen; LDH, lactate dehydrogenase; NC, nonproductive cough; F, fever; D, dyspnea; CP, chest pain; and PC, productive cough.

†Patient receiving supplemental oxygen.

Table 2 summarizes the clinical presentations of the 11 episodes of PCP. At the time of diagnosis of PCP, pulmonary symptoms had been present from 1 to 30 days (median, 7 days). The most common presenting symptoms were dyspnea in eight cases and a nonproductive cough in seven. Fever was present in six of the episodes. In nine episodes in which an arterial blood gas value was obtained, an increased alveolar-arterial oxygen tension gradient (range, 23.5 to 215 mm Hg; median, 54 mm Hg) was present. One arterial blood gas value was obtained from a patient receiving supplemental oxygen (episode 5, Table 2). Elevated lactate dehydrogenase (LDH) levels ranged from 336 to 1284 U/L (median, 510 U/L), and were present in each episode. Serum albumin level ranged from 24 to 38 g/L. Total leukocyte count at diagnosis of PCP ranged from 3.5 to 14.4×10^9/L, and absolute lymphocyte counts ranged from 0.17 to 2.3×10^9/L (median, 0.28×10^9/L; lower limit of normal is 1.0×10^9/L). Chest roentgenograms at the time of the initial pulmonary evaluation showed either no infiltrate (episode 8), or infiltrates that were focal, bilateral (multifocal), or diffuse. A cavitary lesion in addition to infiltrates was seen in one case (episode 3).

Fiberoptic bronchoscopy was diagnostic in each of the eight cases in which it was performed. Bronchoalveolar lavage analysis was positive for PCP in six of eight patients. A transbronchial biopsy specimen was positive in three of the six patients who had this procedure. Two patients (episodes 10 and 11) were found to have more than one pulmonary pathogen. The first patient (episode 10) underwent bronchoscopy because of a nonproductive cough, chest pain, and a persistent infiltrate on chest roentgenography. *Pneumocystis carinii* was found in the bronchoalveolar lavage, and fungal elements consistent with *Aspergillus* sp were found invading blood vessels in the transbronchial biopsy specimens. The second patient (episode 11) had autopsy lung cultures and histologic findings consistent with cytomegalovirus infection as well as PCP. Three patients did not undergo bronchoscopy but received diagnoses at autopsy. One of these (episode 5) had a fulminant clinical course and died on the day of admission before any procedure could be carried out; the second (episode 9) was taking anticoagulants and died before the prothrombin time returned to normal, preventing bronchoscopy; the third (episode 11) was moribund from progressive tumor when pulmonary symptoms began, and at the family's request, bronchoscopy was not performed.

Ten episodes were treated with intravenous trimethoprim-sulfamethoxazole. None of these patients had an adverse reaction to therapy. All were receiving dexamethasone throughout therapy.

Four patients (40%) died of PCP. Six patients survived seven episodes of PCP; five subsequently died of their tumors.

Forty Patients Without PCP

It is difficult to determine the exact incidence of PCP in a setting in which patients are often seen in initial evaluation and then referred back to their point of origin while still receiving corticosteroid therapy. Five hundred eighty-seven adult patients with primary brain tumors were seen for therapy at MSKCC from 1981 to 1989. The records of 40 patients from this group were reviewed to determine how many received ongoing treatment there. Four did not receive therapy at MSKCC or had less than 1 month of follow-up. Therefore, we estimated that 90% of the total study group had received ongoing treatment. This would make 1.7% a least estimate of the percentage of patients in whom PCP developed. All 40 patients received steroid therapy, with durations (to discontinuation of steroid therapy or to last follow-up) ranging from 3 weeks to 28 months (median, 3.8 months).

COMMENT

The association between PCP and the use of high doses of corticosteroids is well documented. Data available in the literature suggest that steroids permit reactivation of latent infection by suppressing the immune system of the host.[9,10] Cellular immunity seems to play the predominant role in the host's defenses against PCP. Many of the underlying diseases in patients with PCP have associated defects of cellular immunity.[1-5] Cyclosporine[11] and dexamethasone both predispose patients to PCP and both inhibit T-lymphocyte proliferation by mechanisms affecting interleukin 2 (T-cell growth factor), a T-helper cell product.[12,13] Single doses of glucocorticoids in humans have been shown to induce peripheral lymphopenia, probably by redistribution of lymphocytes from the circulation into other body compartments.[14] None of our patients had tests of immunologic function, but peripheral lymphopenia was present in all for whom this information was available.

Paradoxically, PCP often becomes clinically apparent when steroid doses are being decreased or withdrawn. Animal studies suggest that a tapering of steroid therapy may simply unmask *P carinii* infections that have developed earlier during high-dose steroid administration. In a rat model, steroids have depressed the capability of the host to mount an inflammatory response to *P carinii* infection. This inflammatory response appears as the steroid dosage is decreased.[9] Those rats receiving high-dose steroids in which PCP developed had scanty alveolar exudates despite the presence of *P carinii* organisms in the lung tissue. When steroids were withdrawn or tapered, intense inflammatory exudates developed. Similarly, rabbits on long-term, stable steroid doses suffer PCP without the characteristic proteinaceous alveolar exudate and interstitial plasma cell infiltration.[10]

Multiple human studies have confirmed the relationship between decreasing steroid doses and PCP. Fossieck and Spagnolo[6] observed the appearance of PCP in patients with lung cancer who were receiving tapering doses of steroids. Other investigators have found that of 19 children with cancer in whom PCP developed, 17 had recently had steroid administration discontinued or were receiving low-dose replacement therapy when the diagnosis of PCP was made.[15] Singer et al[16] reported the occurrence of PCP in 11 patients (10 with lymphoma or leukemia) who had received steroid therapy. In seven of these patients, PCP developed in the setting of a tapering of steroid therapy. In our series, eight of 11 episodes of PCP occurred during a tapering of steroid therapy. The duration of the tapering of steroid therapy before the onset of pulmonary symptoms ranged from 1 to 63 days, but seven of the episodes occurred within 21 days of initiation of the tapering.

In all prior studies, PCP was rare among patients with solid tumors. Our findings, however, suggest that this disease occurs in a subset of patients with solid tumors, namely, those with brain tumors. The increased incidence of PCP in patients with primary brain tumors is most likely due to the fact that they frequently receive high-dose corticosteroids for extended periods. Patients with solid tumors that do not arise in the central nervous system who are placed on similar steroid regimens may also be at risk for PCP. In the only other published series of patients with solid tumors who had PCP, three of five patients with lung cancer who had PCP had received dexamethasone for brain metastases, followed by a tapering of steroid therapy.[6]

Clinicians should have a high index of suspicion for PCP in this selected patient population, particularly because the clinical presentation of PCP can be subtle and nonspecific. Patients with mild pulmonary symptoms in whom the diagnosis of PCP is suspected should be screened carefully. If the chest roentgenogram shows diffuse infiltrates, bronchoscopy should be done emergently. If the chest roentgenogram is normal and the patient has mild symptoms, other sensitive tests might be helpful to detect interstitial lung disease. These tests include pulmonary diffusing capacity,[17,18] rest and exercise arterial blood gas values,[19] or performance of a gallium citrate lung scan.[20] If any of these test results are abnormal, one should proceed to bronchoscopy. A serum LDH measurement may be useful. All the patients in this study had elevated levels of LDH. A previous report on patients with acquired immunodeficiency syndrome (AIDS) who had PCP found that only 7% had normal LDH levels, and levels greater than 450 U/L were highly specific for PCP.[21] In this same study, six (75%) of eight patients without AIDS with PCP had elevated LDH levels. Further investigation is required to determine the sensitivity and specificity of this test in the population without AIDS. Confirmation of the diagnosis of PCP depends on the demonstration of the organisms either in lung tissue or in bronchoalveolar lavage fluid.

If abnormalities consistent with the diagnosis are found in any of the above tests, further evaluation with bronchoscopy, including bronchoalveolar lavage[8,22] and transbronchial biopsy,[23,24] is recommended. In more acutely ill patients, bronchoscopy is recommended to make the diagnosis as rapidly as possible. If bronchoscopy is nondiagnostic, the decision as to whether the patient should have an open-lung biopsy, close follow-up, or empirical therapy depends on the clinical status of the patient and the physician's index of suspicion.

In a prospective, randomized study of children with hematologic malignant neoplasms, trimethoprim-sulfamethoxazole provided excellent protection against PCP with minimal toxic reaction.[25] In a second study of this population, trimethoprim-sulfamethoxazole prophylaxis had equal efficacy when administered for 3 consecutive days each week when compared with a daily regimen.[26] Although the risk of PCP in these studies was much higher than in our patients (PCP developed in 17 of the 80 patients in the placebo-treated group), our findings suggest that prolonged administration of high doses of steroids in patients with brain tumors substantially increases the risk of PCP.

Patients likely to need prolonged, high-dose steroid therapy include those with large postoperative tumor burdens, those in whom steroid dependence develops during radiotherapy, and those with unresectable brain-stem lesions. Such patients undergoing tapering of steroid therapy are a high-risk subgroup. Given the high mortality of 36%, trimethoprim-sulfamethoxazole prophylaxis should be considered for such patients.

References

1. Burke BA, Good RA. *Pneumocystis carinii* infection. *Medicine*. 1973;52:23-51.
2. Sheldon WH. Pulmonary *Pneumocystis carinii* infection. *J Pediatr.* 1962;61:780-791.
3. Hartman B, Koss M, Hui A, Baumann W, Athos L, Boylen T. *Pneumocystis carinii* pneumonia in the acquired immuno-deficiency syndrome (AIDS): diagnosis with bronchial brushings, biopsy and bronchoalveolar lavage. *Chest*. 1987;87:603-607.
4. Rifkind D, Faris TD, Hill RB. *Pneumocystis carinii* pneumonia: studies on the diagnosis and treatment. *Ann Intern Med*. 1966;65:943-956.
5. Peters SG, Prakash UBS. *Pneumocystis carinii* pneumonia. *Am J Med*. 1987;82:73-78.
6. Fossieck BE, Spagnolo SV. *Pneumocystis carinii* pneumonitis in patients with lung cancer. *Chest*. 1980;78:721-722.
7. Oster MW, Vizel M, Edsall JR, Barron BA. Case report: *Pneumocystis* pneumonia in a patient with cervical carcinoma treated with combination chemotherapy. *Gynecol Oncol*. 1982;13:262-264.
8. Stover DE, Zaman MB, Hajdu SI, Lange M, Gold J, Armstrong D. Bronchoalveolar lavage in the diagnosis of diffuse pulmonary infiltrates in the immunosuppressed host. *Ann Intern Med*. 1984;101:1-7.
9. Frenkel JK, Good JT, Shultz JA. Latent *Pneumocystis* infection of rats, relapse, and chemotherapy. *Lab Invest*. 1966;15:1559-1577.
10. Sheldon WH. Experimental pulmonary *Pneumocystis carinii* infection in rabbits. *J Exp Med*. 1959;110:147-160.
11. Hughes WT, Smith B. Provocation of infection due to *Pneumocystis carinii* by cyclosporin A. *J Infect Dis.* 1982;145:767.
12. Larsson EL. Cyclosporin A and dexamethasone suppress T cell responses by selectively acting at distinct sites of the triggering process. *J Immunol*. 1980;124:2828-2832.
13. Arya SK, Wong-Staal F, Gallo RC. Dexamethasone-mediated inhibition of human T cell growth factor and gamma-interferon messenger RNA. *J Immunol*. 1984;133:273-276.
14. Fauci AS, Dale DC. The effect of in vivo hydrocortisone on subpopulations of human lymphocytes. *J Clin Invest*. 1974;53:240-246.
15. Johnson HD, Johnson WW. *Pneumocystis carinii* pneumonia in children with cancer: diagnosis and treatment. *JAMA*. 1970;214:1067-1073.
16. Singer C, Armstrong D, Rosen PP, Schottenfeld D. *Pneumocystis carinii* pneumonia: a cluster of eleven cases. *Ann Intern Med*. 1975;82:772-777.
17. Nisam M, Wong S, Fallat RJ. Pulse oximetry and diffusing capacity in AIDS patients with *Pneumocystis carinii* pneumonia. *Chest*. 1987;92:134S. Abstract.
18. Sankary RM, Turner J, Lipavsky A, Howes EL, Murray JF. Alveolar-capillary block in patients with AIDS and *Pneumocystis carinii* pneumonia. *Am Rev Respir Dis.* 1988;137:443-449.
19. Stover DE, Greeno RA, Gagliardi AJ. The use of a simple exercise test for the diagnosis of *Pneumocystis carinii* pneumonia in patients with AIDS. *Am Rev Respir Dis.* 1989;139:1343-1346.
20. Barron TF, Birnbaum NS, Shane LB, Goldsmith SJ, Rosen MJ. *Pneumocystis carinii* pneumonia studied by gallium-67 scanning. *Radiology.* 1985;154:791-793.
21. Zaman MK, White DA. Serum lactate dehydrogenase levels and *Pneumocystis carinii* pneumonia: diagnostic and prognostic significance. *Am Rev Respir Dis.* 1988;137:796-800.
22. Drew WL, Finley TN, Mintz L, Klein HZ. Diagnosis of *Pneumocystis carinii* pneumonia by bronchopulmonary lavage. *JAMA*. 1974;230:713-715.
23. Hodgkin JE, Andersen HA, Rosenow EC. Diagnosis of *Pneumocystis carinii* pneumonia by transbronchoscopic lung biopsy. *Chest*. 1973;64:551-554.
24. Springmeyer SC, Silvestri RC, Sale, GE, et al. The role of transbronchial biopsy for the diagnosis of diffuse pneumonias in immunocompromised marrow transplant recipients. *Am Rev Respir Dis.* 1982;126:763-765.
25. Hughes WT, Kuhn S, Chaudhary S, et al. Successful chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med*. 1977;297:1419-1426.
26. Hughes WT, Rivera GK, Schell MJ, Thornton D, Lott L. Successful intermittent chemoprophylaxis for *Pneumocystis carinii* pneumonitis. *N Engl J Med*. 1987;316:1627-1632.

Neuroanatomic Differences Between Dyslexic and Normal Readers on Magnetic Resonance Imaging Scans

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• The areas of six bilateral brain segments in the right and left hemispheres, on a horizontal brain section, and the area of subdivisions of the corpus callosum, on a midsagittal brain section, were measured on magnetic resonance images obtained from 21 dyslexic and 29 control subjects. In the entire group, the frontal half of the horizontal brain section showed asymmetry, with the right side being larger, whereas posteriorly only the occipital polar segment was asymmetrical, with the left side being larger. Dyslexic subjects exhibited asymmetry, with the right side greater than the left side, in contrast to the relatively symmetrical pattern that is normally observed in the midposterior segment that corresponds to the angular gyrus. In the corpus callosum, dyslexic subjects were found to have a larger splenium than nondyslexic subjects, and dyslexic female subjects were found to have a larger splenium than dyslexic male subjects. Because transcallosal pathways connecting the left and right angular gyrus regions traverse through the splenium of the corpus callosum, the above findings in dyslexic subjects suggest an anatomic abnormality in the angular gyrus region.

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There now exists a strong body of evidence that the human cerebral hemispheres are morphologically asymmetrical in adults as well as in children.[1] As a discrete structure in the brain, the posterior portion of the superior temporal plane (the planum temporale) shows an impressive left-greater-than-right asymmetry, but other structures, such as the frontal lobes, have also been shown to be consistently asymmetrical at a macroscopic level.[1] Cytoarchitectonic studies show asymmetries with greater neuronal density on the left side in the inferior parietal lobe,[2] the left auditory cortex,[3] and the posterior portion of the thalamus.[4]

Some of these morphologic asymmetries may be linked to functional differences between the hemispheres. For example, it has been postulated that because the left planum temporale, which is located in Wernicke's area, is larger than the right in 65% of adult brains, the larger left planum is in some way related to left hemispheric dominance for language.[5,6] Furthermore, neuropathologic studies in four adult dyslexic subjects who have exhibited symmetry of the plana temporale, rather than the usual asymmetry, also suggest an association between the relative asymmetry of this structure and functional abilities in the language domain.[7] Direct evidence linking anatomic asymmetries to language laterality or other functional differences between the two hemispheres, however, is still lacking.[8,9]

Geshwind[10] suggested that the information obtained from studies of cases of acquired dyslexia could be useful to obtain an understanding of the neurologic basis of developmental dyslexia. In this regard, it is clear, beginning with the earliest studies of Dejerine,[11] that lesions in the left angular gyrus are associated with alexia, among other findings. More recently, Benson[12] categorized alexias, by the sites of the causative lesions and the clinical presentations, into posterior alexia (occipital alexia or alexia without agraphia), central alexia (parietotemporal alexia or alexia with agraphia), and anterior alexia (frontal alexia or motor alexia associated with Broca's aphasia). In addition to the left angular gyrus, the medial occipital lobes, and Broca's area, the splenium of the corpus callosum has also been implicated in posterior alexia.[13] (Studies involving reading-disabled children show evidence of inefficient interhemispheric transfer of visual information, which would also suggest that the splenium of the corpus callosum may be at fault.[14,15])

Several neuroimaging studies, with the use of computed tomography (CT), have suggested reduced or reversed asymmetry of the posterior aspects of the cerebral hemispheres in dyslexic subjects,[16-18] although one nonquantitative magnetic resonance imaging (MRI) study has failed to demonstrate any anatomic differences between dyslexic and normal subjects.[19] (For a review of these studies, see Hynd and Semrud-Clikeman.[20])

Planes that cannot be imaged by CT, such as the sagittal plane, can be visualized on MRI scans. With the advent of MRI, it has become possible to obtain much improved definition of neuroanatomic structures. In this study, we compared groups of well-defined, right-handed male and female subjects and dyslexic and normal readers on measures of cerebral anatomic asymmetry and corpus callosum size, obtained by area measurements on MRI scans. Area measurements constitute an advance over previously reported linear measurements, although true volumetric analysis would have been preferable. This was deemed impractical for this study because three-dimensional reconstruction of anatomic regions was not available to us with the system that was used.

We chose to segment the brain into six pairs of areas that corresponded to brain regions of interest to define the location of these asymmetries. A single section in the horizontal plane, at the level of the foramen of Monro, includes most brain regions that are considered important for reading and language.[13] Previous studies have involved evaluation of brain asymmetries via transverse linear measurements at arbitrarily chosen points along the anteroposterior dimension of the brain. In this study, we categorized the brain regions where these asymmetries were most prominent and where they best discriminated between groups of subjects, ie, male vs female subjects and dyslexic vs normal readers. Based on previous neuroimaging findings in subjects with developmental language disorders,[16-18] the working hypothesis in this study was that one or more brain segments in the posterior half of the brain would show aberrant asymmetry in dyslexic subjects.

METHODS

MRI

Magnetic resonance imaging was performed with a superconducting whole-body scanner (Siemens Magnetom, Iselin, NJ) (1.0 or 1.5 T) with use of a 25-cm-diameter head coil. Sections were 7.0 mm thick, with 3.0 mm intersection intervals with use of a 256 × 512-pixel matrix. Three sagittal T_1-weighted spin-echo sequences (repetition time, 500 milliseconds; echo time, 17 milliseconds) were obtained with the central section positioned through the midline. Transverse T_2-weighted spin-echo sequences (repetition time, 2500 milliseconds; echo time, 25 and 90 milliseconds) provided 13 sections that were obtained parallel to the inferior orbitomeatal plane with one section transecting the foramen of Monro. The correct plane was ensured by appropriate positioning of the patient before the study began. The measurements on the horizontal section were performed on the T_2-weighted image, with an echo time of 25 milliseconds (proton density image).

Measurements

All measurements were made with a planimeter on brain outlines derived from hand tracings of MRI scans.

Horizontal Areas.—Horizontal area measurements were made from transverse MRI scans at the level of the foramen of Monro. This section is anatomically very similar across subjects in that it transects the basal ganglia, thalamus, and the four tips of the lateral ventricle horns (Fig 1). This section is very informative for this study, as it includes parts of the prefrontal and premotor lobules of the frontal lobe (including Broca's area), the superior temporal gyrus, the inferior parietal lobule, and the cuneus and lateral cortex of the occipital lobe (level 6 in the brain according to the atlas by Eycleshymer and Schoemaker,[21] which is also sectioned in the inferior orbitomeatal line).

The brain was traced along the inner table of the skull, and a line was drawn along the interhemispheric fissure following its contours. The anterior and posterior limits of this line were determined as the points at which there was divergence of the medial outlines of each hemisphere in the frontal and occipital regions. The length of the interhemispheric line was based on the linear distance between these two points. The segmentation of the brain (see below) was based on the linear distance, but the area measurements were performed with the contoured medial border, which was the interhemispheric fissure. The interrater reliability of the placement of the anterior and posterior limits of the interhemispheric line was determined by having two raters (R.D. and A.K.) determine these points on tracings of the brain and measure the distance from these points to a fixed point. The correlation coefficients were .95 and .98, respectively, for the anterior and posterior limits. Lines were drawn perpendicular to the midline at its midpoint (50% line) and at 10% and 30% distances from the anterior and posterior limits, dividing the brain into six pairs of right- and left-sided brain segments (Fig 1). These segments were designated anterior polar 10%, midanterior 20%, anterior central 20%, posterior central 20%, midposterior 20%, and posterior polar 10%. Each area measurement was made three times, and the mean value was used. Interrater reliabilities for these mean values among three raters were $r = .98$ and $r = .99$. On the lateral surface of the brain, the cerebral cortex in the anterior polar 10% corresponded approximately to prefrontal regions; midanterior 20% to premotor regions, including Broca's area; anterior central 20% to the insular cortex and the anterior part of the superior temporal gyrus; posterior central 20% to the plana temporale (or the posterior part of the superior temporal gyrus) and the supramarginal gyrus of the inferior parietal lobe; midposterior 20% to the angular gyrus; and posterior polar 10% to the lateral occipital cortex and the cuneus of the occipital lobe. This correspondence of anatomic brain regions to the segments used in this study was ascertained by segmentation of the brain section at the appropriate axial level (level 6) according to the atlas by Eycleshymer and Schoemaker.[21] It was then possible to determine, on both the lateral surface of the brain, provided in the atlas, and on the horizontal section, the brain regions encompassed by each segment. The area of each right and left half of the individual segments contributed the primary data for this analysis.

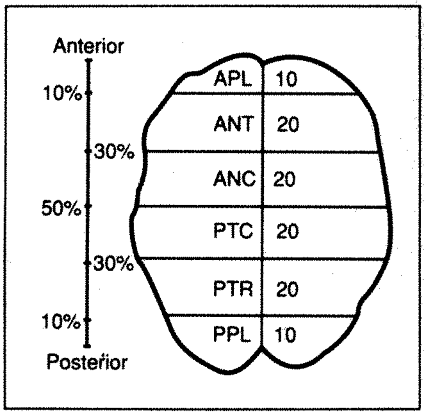

Fig 1.—Drawing of horizontal brain section in dyslexic subjects and nondyslexic subjects with the location and extent of each of six segments. APL indicates anterior polar; ANT, anterior; ANC, anterior central; PTC, posterior central; PTR, posterior; and PPL, posterior polar.

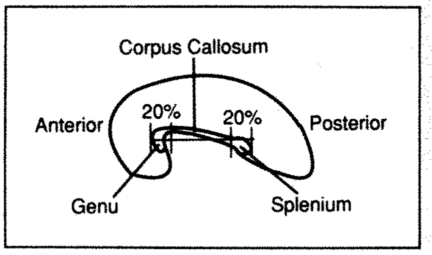

Fig 2.—Drawing of sagittal brain section, with depiction of the outlines of the corpus callosum and its subdivisions and the midsagittal brain area.

Corpus Callosum Areas.—Corpus callosum measurements were made from sagittal MRI scans of the midsagittal plane. The corpus callosum was traced directly. The midsagittal brain area was traced by following the superior border of the corpus callosum from the genu to the splenium and then following the cerebrum posteriorly along the inferior border of the occipital lobe and continuing anteriorly over the convexity of the brain and finally posteriorly along the inferior border of the frontal lobe until the genu was reached again (Fig 2). The corpus callosum was divided into fifths along a line joining the most anterior and posterior points on the genu and the splenium, respectively. Area measurements were made of the total corpus callosum, anterior fifth or genu, and posterior fifth or splenium. Each callosal area was normalized to and expressed as a percentage of the midsagittal brain area to control for individual differences in brain size.

Informed consent was obtained from each participant in the study after the procedures were explained. Each prospective subject underwent a clinical interview to obtain information pertinent to diagnosis (ie, developmental, family, and educational history). As dyslexia is thought to have a heterogeneous origin, we sought to minimize variability among dyslexic subjects by confining our sample to individuals with a clear family history in first-degree relatives and to those with no known prenatal or perinatal condition that might yield learning problems. Because of the frequent overlap in the population between dyslexia and attention-deficit–hyperactivity disorder (ADHD), we did not exclude dyslexic subjects who also reported a childhood history of ADHD, for practical reasons. To do so would have added an unacceptable restraint to the subject recruitment process. The stringent criteria for reading and spelling deficits (see below) ensured that no dyslexic subjects had purely ADHD. However, to ensure the normalcy of our control group, normal readers with a history of ADHD or any other learning disability were excluded.

Table 1.—Subject Characteristics

Variables	Mean ± SD Dyslexics	 Nondyslexics
Sex, No.		
M	12	15
F	9	14
Age, y	39.1 ± 11	35.3 ± 10
Education, y	14.3* ± 3	17.7 ± 3
Handedness†	0.80 ± 0.2	0.82 ± 0.2
GORT-R‡ (standard score)	105.0§ ± 18	119.5 ± 15
WRAT-R‖ (standard score)	86.1 ± 14	. . .
WAIS-R¶ (full-scale IQ)	114.4 ± 15	. . .
Nonsense passages#		
Errors	62.6* ± 28	102.7 ± 12
Time	55.7* ± 35	101.3 ± 13

*$P < .001$.

†Handedness per Edinburgh Handedness Inventory[22] (−1.0 indicates left-handed; 0, ambidextrous; and 1.0, right-handed).

‡GORT indicates Gray Oral Reading Test.[23,24]

§$P < .02$.

‖WRAT indicates Wide Range Achievement Test/Spelling.[27,28]

¶WAIS indicates Wechsler Adult Intelligence Scale-Revised.[26]

#Nonsense Passage Reading (standard scores).[25]

A total of 50 right-handed adults participated in the study (Table 1). This study group included 21 dyslexic (12 male and nine female) and 29 nondyslexic (15 male and 14 female) subjects. Handedness was measured by the Edinburgh Handedness Inventory.[22] Groups were matched as closely as possible for age and years of education (Table 1). Because of the disadvantage that dyslexic subjects experienced in acquiring an education, there was a significant difference in the educational levels of the two groups, but all dyslexic subjects were of average to high-average intelligence (Table 1). The diagnosis of developmental dyslexia was made if all the following conditions were met: (1) a 1.5-SD discrepancy on reading and/or spelling tests vs IQ was verified; (2) there existed a history of childhood reading and spelling problems; and (3) there existed a family history of dyslexia in at least two generations.

Dyslexic subjects scored significantly lower than nondyslexic subjects on oral reading of meaningful text (Gray Oral Reading Test[23,24]; $P<.02$) and Nonsense Passages[25] ($P<.001$). Both groups comprised native English-speaking subjects who had neither neurologic nor psychiatric disorders, all of whom reported having had adequate educational opportunity for learning to read.

Severity Scores.—A group of dyslexic subjects (n = 16) was rated on a severity score based on differences on standard scores of full-scale IQ (Wechsler Adult Intelligence Scale-Revised)[26] and certain reading and spelling tests. The severity score comprised the average of three components: (1) full-scale IQ–Gray Oral Reading Test, (2) full-scale IQ–Wide Range Achievement Test (Spelling),[27,28] and (3) full-scale IQ–Average of Nonsense Passage Errors and Trials. The higher the severity score, the greater the relative impairment in reading and spelling.

DATA ANALYSIS

Horizontal brain areas were obtained for the right and left segments of the anterior polar, anterior, anterior central, posterior central, posterior, and posterior polar regions and analyzed with a multivariate analysis of covariance approach. Diagnosis (dyslexic vs normal readers) and gender (male vs female subjects) served as independent grouping factors, while hemisphere (right vs left) was treated as a repeated measure. Because of large individual differences in brain size, total brain area was entered as a covariate in this analysis. A covariate approach was adopted rather than entering normalized measurements into the multivariate analysis of variance equation, as the latter approach would confound the variance-covariance matrix and create extensive interdependence between measures (scores for each patient would necessarily add up to 100% with the use of normalized measures), thus violating necessary assumptions required for these analyses. Whenever significant, multivariate analysis of covariance main effects and/or interactions were obtained ($P<.05$), subsequent univariate analyses of variance (ANOVAs) were then examined. Because of multiple ANOVA contrasts, a more conservative criterion of $P<.01$ was set for each univariate analysis.

To examine the relationship between severity scores and brain areas, whenever a brain segment indicated a significant main effect or interaction on the multivariate analysis of covariance, further analyses utilizing Spearman rank correlations were performed between severity scores and brain segment areas. Again, due to multiple comparisons, the criterion for significance was set at $P<.01$.

Corpus callosum area measurements were analyzed with the use of three separate ANOVAs, with the normalized area measurements for the genu, splenium, and total corpus callosum area as dependent measures and diagnosis and gender serving as independent grouping factors. Criterion for significance was set at $P = .05$ for the ANOVA. Post hoc analyses of any significant main effects or interactions were conducted with the Student-Newman-Keuls procedure, with a criterion for significance set at $P = .05$. Spearman rank correlations were performed between the severity scores and the corpus callosum areas that showed significant main effects or interactions for diagnosis or hemisphere on the ANOVA. Because of multiple comparisons, the α value was set at $P<.01$ for these series of analyses.

RESULTS

Horizontal Area Measurements

Significant main effects for hemisphere ($F[1,45] = 8.83$, $P = .001$) and gender ($F[1,45] = 2.86$, $P = .02$) were obtained, and the diagnosis × hemisphere interaction was also significant ($F[1,45] = 2.49$, $P = .04$). Post hoc analysis of the hemispheric effects revealed that there were highly significant differences in the anterior polar 10% ($P = .001$), midanterior 20% ($P = .001$), and anterior central 20% ($P = .001$) segments, with the right side being larger than the left in these anterior segments. There was also a significant difference in the posterior polar 10% segment ($P = .004$), with the left side being larger than the right (Table 2) (Fig 3). Post hoc analysis of the gender effect revealed significant differences in the combined right and left areas of the midanterior 20% segment ($P = .003$) and the midposterior 20% segment ($P = .001$), where male subjects had larger area measurements than female subjects (Table 3), but there was no gender × hemisphere interaction. Finally, the diagnosis × hemisphere interaction post hoc analysis showed a significant effect only in the midposterior 20% segment ($P = .007$), where the right side of this segment was larger than the left in dyslexic readers, but the left side was slightly larger than the right in normal readers (Table 4). Spearman rank correlations revealed a significant positive correlation ($r = .58$, $P = .005$) between the severity score and the normalized area of the right side of the posterior polar 10% brain segment in dyslexic subjects.

Corpus Callosum Area Measurements

Results are summarized in Table 5 and Fig 4. Total corpus callosum measurement analysis revealed no ANOVA main effects for diagnosis or gender but did reveal a significant diagnosis × gender interaction (F[1,44] = 4.8, $P = .034$). Post hoc analysis revealed that dyslexic female subjects had a larger total corpus callosum area than dyslexic male or normal female subjects. In the genu measurements, there was also a diagnosis × gender interaction in the ANOVA analysis (F[1,44] = 5.12, $P = .029$). Post hoc analysis revealed that dyslexic female subjects had a larger genu area than dyslexic male subjects. Finally, in the splenium there were significant main effects for diagnosis (F[1,44] = 6.9, $P = .012$) (larger in dyslexic subjects) and for gender (F[1,44] = 8.65, $P = .005$) (larger in female subjects), but there was no significant diagnosis × gender effect. Post hoc analysis revealed that dyslexic female subjects had a larger splenial area than dyslexic male subjects, normal female subjects, and normal male subjects, but normal female subjects did not have a larger area than normal male subjects. Spearman rank correlations between severity scores and the relative sizes of the genu, splenium, and total corpus callosum were not significant in dyslexic subjects.

Table 2.—Normalized Horizontal Area Measurements* in All Subjects (Dyslexic and Normal Readers): Hemispheric Differences

Brain Segments	Right Hemisphere	Left Hemisphere	P†
Anterior polar (APL 10)	4.8 ± 0.8	4.4 ± 0.9	.001
Anterior (ANT 20)	9.0 ± 0.7	8.6 ± 0.6	.001
Anterior central (ANC 20)	10.6 ± 0.8	10.2 ± 0.8	.001
Posterior central (PTC 20)	11.3 ± 1.0	11.2 ± 0.7	NS
Posterior (PTR 20)	9.7 ± 0.7	9.7 ± 0.8	NS
Posterior polar (PPL 10)	5.1 ± 1.1	5.4 ± 1.0	.004

*Values are mean ± SD. Value is expressed as a percentage of the total horizontal area of the brain (ie, it is a normalized area to correct for differences in brain size).

†Probability value as determined on univariate (analysis of variance) tests. NS indicates not significant.

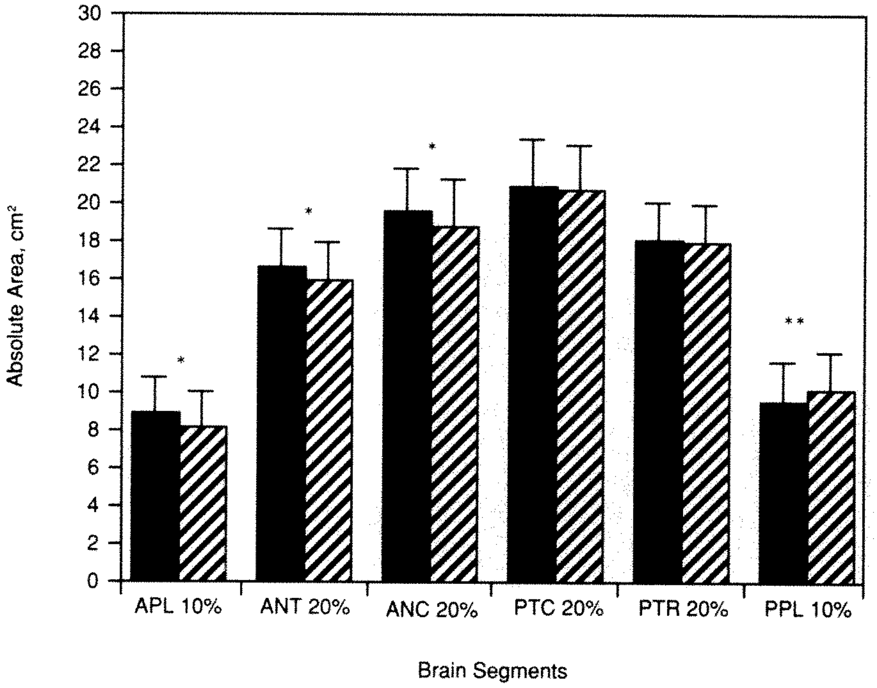

Fig 3.—Horizontal area measurements for various left hemisphere (hatched bars) and right hemisphere (black bars) brain segments in all subjects. See Fig 1 legend for expansions of abbreviations. Single asterisk indicates $P = .001$; double asterisks, $P = .004$.

COMMENT

Modern interest in the asymmetry of the human brain was stimulated by Geschwind and Levitsky[5] in their report that the length of the planum temporale measured in postmortem adult brains was asymmetrical and usually greater on the left side. A further report of asymmetry in the planum temporale, for both adult and infant human postmortem brains, was made by Wada et al,[29] and left-sided predominance was confirmed. In the frontal operculum, Wada et al found the right side to be larger than the left. LeMay and Kido[30] evaluated CT scans in right-handed subjects and reported left occipital petalia (indenting of the inner table of the skull) in about two thirds of their sample. While they found symmetry to be common in the frontal regions, 30% of their sample evidenced right frontal petalia and only 7% evidenced left frontal petalia. Other studies have confirmed these findings.[31-34]

Our results demonstrate that in quantitative area analyses of six bilateral brain regions, systematic asymmetry occurs in anterior and posterior brain regions. We have shown that the anterior three segments (corresponding to prefrontal, premotor, and insular cortex/superior temporal gyrus) are asymmetrical, with the right side being larger than the left, whereas in the posterior half of the brain, only the posterior polar 10% region, corresponding to the cuneus and lateral occipital lobe, is asymmetrical, with the left side being larger than the right. The region of the brain that includes most of the planum temporale, ie, the posterior central 20% segment, was found to be symmetrical in our study.

We were unable to find a gender difference in brain asymmetry, as described by Bear et al,[34] who reported a difference in degree of asymmetry with use of linear measurements in both frontal and occipital lobes, with female subjects exhibiting more symmetry than male subjects. The only gender differences we found were relative increases in male subjects in the size of the whole midanterior 20% region (encompassing the premotor region) and the midposterior 20% region (encompassing the angular gyrus). These differences between the findings of Bear et al[34] and our own may be related to the fact that we made area rather than linear measurements. Whether these anatomic differences are consistent and can be associated with

Table 3.—Horizontal Area Measurement* in All Subjects (Dyslexic and Normal Readers): Gender Differences

Brain Segments	Female	Male	*P*†
Anterior polar (APL 10)			
R	4.8 ± 0.8	4.8 ± 0.9	NS
L	4.4 ± 0.9	4.3 ± 1.0	
Anterior (ANT 20)			
R	8.8 ± 0.9	9.2 ± 0.5	.003‡
L	8.5 ± 0.8	8.7 ± 0.4	
Anterior central (ANC 20)			
R	10.6 ± 0.8	10.6 ± 0.8	NS
L	10.5 ± 0.9	10.0 ± 0.7	
Posterior central (PTC 20)			
R	11.2 ± 1.1	11.3 ± 0.8	NS
L	11.4 ± 0.8	11.0 ± 0.7	
Posterior (PTR 20)			
R	9.6 ± 0.8	9.8 ± 0.5	.001‡
L	9.5 ± 0.9	9.8 ± 0.6	
Posterior polar (PPL 10)			
R	5.2 ± 0.9	5.0 ± 1.2	NS
L	5.4 ± 0.8	5.4 ± 1.2	

*Values are mean ± SD. Value is expressed as a percentage of the total horizontal area of the brain.

†Probability value as determined on univariate (analysis of variance) test. NS indicates not significant.

‡Differences are between female and male subjects (gender effect) across hemispheres (no hemispheric effect).

Table 4.—Horizontal Area Measurement* in Dyslexic and Normal Readers

Brain Segments	Dyslexic Readers	Normal Readers	*P*†
Anterior polar (APL 10)			
R	4.7 ± 0.6	4.9 ± 1.0	NS
L	4.3 ± 0.7	4.5 ± 1.1	
Anterior (ANT 20)			
R	8.9 ± 0.9	9.1 ± 0.6	NS
L	8.6 ± 0.7	8.7 ± 0.6	
Anterior central (ANC 20)			
R	10.6 ± 0.8	10.6 ± 0.8	NS
L	10.2 ± 0.9	10.2 ± 0.8	
Posterior central (PTC 20)			
R	11.5 ± 1.0	11.1 ± 0.9	NS
L	11.3 ± 0.9	11.1 ± 0.6	
Posterior (PTR 20)			
R	9.9 ± 0.7	9.6 ± 0.7	.006‡
L	9.6 ± 0.7	9.7 ± 0.8	
Posterior polar (PPL 10)			
R	5.2 ± 1.2	5.0 ± 1.0	NS
L	5.4 ± 1.0	5.5 ± 1.0	

*Values are mean ± SD. Value is expressed as a percentage of the total horizontal area of the brain.

†Probability value as determined on univariate (analysis of variance) test. NS indicates not significant.

‡Differences are right-sided relative to left-sided values in dyslexic vs normal readers (diagnosis by hemispheric interactions only).

language or reading function will have to be determined in future studies.

Hier et al[16] studied 24 dyslexic subjects (two women, six "left-handed") with the use of CT of the brain. They observed that 10 dyslexic subjects had reversal of the usual left-greater-than-right asymmetry of posterior portions of the cerebral hemispheres; asymmetry was measured on a line drawn 5 mm anterior to the inner table of the skull at the occipital pole. These 10 subjects with reversed asymmetry had lower mean verbal IQ scores than the remaining 14 dyslexic subjects with either symmetrical posterior cerebral regions (six subjects) or the usual left-greater-than-right asymmetry (eight subjects). Haslam et al[18] evaluated brain CT scans in 26 right-handed boys (9 to 13 years of age) with developmental dyslexia and in eight right-handed boys, who were controls, using methods similar to those of Hier et al.[16] They found a lower-than-expected incidence of left-greater-than-right occipital asymmetry in the dyslexic group.

In our studies, the brain segment on the horizontal section that differentiated dyslexic and normal readers was midposterior 20%, which encompassed mainly the angular gyrus. The right side of this segment was found to be larger than the left in dyslexic subjects but symmetrical in nondyslexic subjects. It was also of interest that the region of the planum temporale, located within the posterior-central 20% segment, was not significantly different between dyslexic and nondyslexic subjects. The dyslexia severity score was found to correlate significantly with the area of the posterior polar 10% segment. This result indicated that the more severe the dyslexia, the larger the area of the right side of this segment.

Taken together, the above findings suggest that the major anatomic abnormality in dyslexic subjects is in two neighboring areas in the posterior part of the brain, encompassing mainly the angular gyrus and the posterior pole. This region tends to be larger than normal on the right side in dyslexic subjects. This finding is consistent with those of Hier et al[16] and Haslam et al,[18] even though these authors were unable to identify the brain regions that caused the differences between subject groups. It is these same structures that were found to be the most consistent sites of abnormality causing acquired alexia.[11,13]

In corpus callosum measurements, we found the splenium to be the region in this structure that showed the major findings of differences between genders and diagnostic groups. The splenium was larger in dyslexic female subjects than in dyslexic male subjects and larger in dyslexic than in normal readers. Little is currently known about the relationship between corpus callosum size and cognitive or functional abilities, although many theories abound. De Lacoste-Utamsing and Holloway[35] found the splenium of the corpus callosum to

Table 5.—Corpus Callosum Area Measurements* in Dyslexic and Normal Readers

	Normal Readers		Dyslexic Readers		
	Female (n = 14)	**Male (n = 15)**	**Female (n = 9)**	**Male (n = 10)**	**Analysis of Variance Results**
Total corpus callosum	6.5±0.6	6.6±0.9	7.5±0.9	6.5±1.2	Diagnosis × gender interaction ($P = .034$)
Genu	2.2±0.4	2.0±0.4	2.4±0.3	2.0±0.3	Diagnosis × gender interaction ($P = .029$)
Splenium	1.8±0.2	1.7±0.3	2.2±0.4	1.8±0.4	Diagnosis effect ($P = .012$) Gender effect ($P = .005$)

*Values, unless otherwise noted, are mean ± SD. Value is expressed as a percentage of the midsagittal brain area.

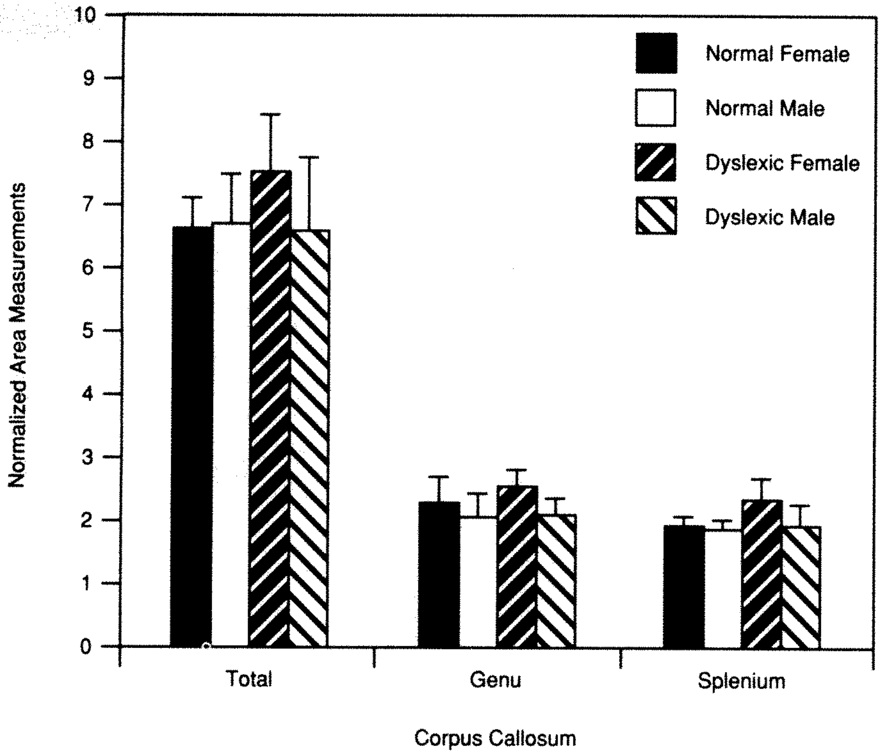

Fig 4.—Corpus callosum measurements (normalized to midsagittal brain area) in dyslexic and nondyslexic male and female subjects).

be larger in five female than in nine male subjects. They speculated that greater hemispheric specialization in male subjects, for visuospatial function, was linked to the smaller size of the male splenium. Although these gender differences in splenium size were not confirmed by Bleier et al[36] in 17 men and 22 women studied with MRI, these authors did not appear to have controlled for overall brain size. Witelson[37] evaluated the corpus callosum in 42 postmortem brains (12 male and 30 female; 27 consistent right-handers and 15 mixed-handers). She found that there was no sexual dimorphism in the size of the corpus callosum or any of its subdivisions but that mixed-handers had larger corpora callosa than consistent right-handers. This finding once again raised the issue of hemispheric specialization of function and corpus callosum size. Those with presumably less hemispheric specialization (mixed-handers) had larger corpora callosa. The size and shape of the corpus callosum appears to be at least partly under genetic control, as the variability of corpus callosum size is much less in monozygotic twin pairs than in randomly paired controls.[38]

With regard to gender differences in the size of the splenium, our results support those of De Lacoste-Utamsing and Holloway.[35] Our findings in dyslexic and normal subjects, however, are unique. The larger splenium that we found in dyslexic subjects would seem to fit well with the finding of an abnormality in the midposterior 20% segment in dyslexic subjects. Transcallosal pathways for the midposterior 20% region (angular gyrus) appear to be located in the splenium of the corpus callosum.[39] The basic assumption here is that reversed anatomic asymmetry in a brain region is associated with a greater degree of bihemispheric distribution of functions normally ascribed to that region. If this is correct, it may also suggest that the portion of the corpus callosum connecting the right and left halves of those brain regions will need to be larger to handle the greater amount of "cross-talk" required between these brain regions. No correlation was found, however, between the size of the splenium and the degree of asymmetry of the midposterior 20%, posterior central 20%, or posterior polar 10% segments ($r = .218$, $P = .10$; $r = -.05$, $P > .25$; $r = -.05$, $P > .25$, respectively). Thus, if there is a relationship between anatomic asymmetry of specific brain regions and the size of the corresponding segment of the corpus callosum, it is not a simple one. Nevertheless, the larger size of the splenium in dyslexic subjects does appear to add to the results obtained from horizontal section measurements. These results together suggest an anatomic abnormality in the posterior half of the brain.

In conclusion, we have shown that (1) the human brain is asymmetrical in the anterior half and the posterior pole; (2) male subjects have relatively larger brain segments than female subjects in a midfrontal and a midposterior location, representing the premotor and angular gyrus regions, respectively; (3) dyslexic subjects tend to have reversed brain asymmetry in a midposterior brain segment corresponding to the angular gyrus; (4) dyslexic subjects have a larger splenium of the corpus callosum than do normal readers; and (5) female dyslexic subjects have a larger splenium than do male dyslexic subjects. The functional importance of these findings will be better understood when correlated with markers of lateralized behaviors, as measured by psychophysical tests and neuropsychological tests, regional cerebral blood flow or metabolism, and brain electrical potentials.

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References

1. Geschwind N, Galaburda AM. Cerebral lateralization: biological mechanisms, associations, and pathology, I: a hypothesis and a program for research. *Arch Neurol.* 1985;42:428-459.

2. Eidelberg D, Galaburda AM. Inferior parietal lobule: divergent architectonic asymmetries in the human brain. *Arch Neurol.* 1984;41:843-852.

3. Galaburda A, Sanides F. Cytoarchitectonic organization of the human auditory cortex. *J Comp Neurol.* 1980;190:597-610.

4. Eidelberg D, Galaburda AM. Symmetry and asymmetry in the human posterior thalamus, I: cytoarchitectonic analysis in normal persons. *Arch Neurol.* 1982;39:325-332.

5. Geschwind N, Levitsky W. Human brain: left-right asymmetries in the temporal speech region. *Science.* 1968;161:186-187.

6. Geschwind N. Cerebral dominance and anatomic asymmetry. *N Engl J Med.* 1972;287:194-195.

7. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive cortical anomalies. *Ann Neurol.* 1985;18:222-233.

8. Henderson VW, Naeser MA, Weiner JM, Pieniaz JM, Chui HC. CT criteria of hemisphere asymmetry fail to predict language laterality. *Neurology.* 1984;34:1086-1089.

9. Naeser MA. Relationship between hemispheric asymmetries on computed tomography scan and recovery from aphasia. *Semin Neurol.* 1984;4:136-150.

10. Geshwind N. The anatomy of acquired disorders of reading. In: Money J, ed. *Reading Disability: Progress and Research Needs in Dyslexia.* Baltimore, Md: The Johns Hopkins Press; 1962.

11. Dejerine J. Contribution á l'étude anatomopathologique et clinique des differentes varietés de cecité verbale. *Memoires Soc Biol.* 1892;4:61-90.

12. Benson F. The third alexia. *Arch Neurol.* 1977;34:327-331.

13. Damasio AR, Damasio H. The anatomic basis of pure alexia. *Arch Neurol.* 1983;33:1573-1583.

14. Gross K, Rothenberg S, Schottenfeld, Drake C. Duration thresholds for letter identification in left and right visual fields for normal and reading-disabled children. *Neuropsychologica.* 1978;16:709-715.

15. Gross-Glenn K, Rothenberg S. Evidence for deficit in interhemispheric transfer of information in dyslexic boys. *Int J Neurosci.* 1984;24:23-35.

16. Hier DB, LeMay M, Rosenberger PB, Perlo VP. Developmental dyslexia: evidence for a subgroup with a reversal of cerebral asymmetry. *Arch Neurol.* 1978;35:90-92.

17. Rosenberger PG, Hier DB. Cerebral asymmetry and verbal intellectual deficits. *Ann Neurol.* 1980;8:300-304.

18. Haslam RHA, Dalby JT, Johns RD, Rademaker AW. Cerebral asymmetry in developmental dyslexia. *Arch Neurol.* 1981;38:679-682.

19. Rumsey JM, Dorwart R, Vermess M, Deukla MB, Kruesi MJP, Rapoport JL. Magnetic resonance imaging of brain anatomy in severe developmental dyslexia. *Arch Neurol.* 1986;43:1045-1046.

20. Hynd GW, Semrud-Clikeman M. Dyslexia and brain morphology. *Psychol Bull.* 1989;106:447-482.

21. Eycleshymer AC, Schoemaker DM. *A Cross-Section Anatomy.* East Norwalk, Conn: Appleton-Century-Crofts; 1976.

22. Oldfield RC. The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia.* 1971;9:97-113.

23. Gray WS. *Gray Oral Reading Test.* Indianapolis, Ind: Bobbs-Merrill Co Inc; 1967.

24. Weiderholt JL, Bryant BR. *Gray Oral Reading Test Revised.* Austin, Tex: Pro-Ed; 1986.

25. Finucci JM, Guthrie JT, Childs AL, Abbey H, Childs B. The genetics of specific reading disability. *Ann Hum Genet.* 1976;40:1-23.

26. Wechsler D. Wechsler Adult Intelligence Scale-Revised. San Antonio, Tex: Psychological Corp; 1981.

27. Jastak JF, Jastak S. *Wide Range Achievement Test.* Wilmington, Del: Jastak Associates; 1978.

28. Jastak S, Wilkinson GS. *Wide Range Achievement Test-Revised.* Wilmington, Del: Jastak Associates; 1984.

29. Wada JA, Clarke R, Hamm A. Cerebral hemisphere asymmetry in humans: cortical speech zones in 100 adult and 100 infant brains. *Arch Neurol.* 1975;32:239-246.

30. LeMay M, Kido DK. Asymmetries of the cerebral hemispheres on computed tomograms. *J Comput Assist Tomogr.* 1978;2:471-476.

31. Chui HC, Damasio AR. Human cerebral asymmetries evaluated by computed tomography. *J Neurol Psychiatry.* 1980;43:873-878.

32. Weinberger DR, Luchins DJ, Morihisa J, Wyatt RJ. Asymmetrical volumes of the right and left frontal and occipital regions of the human brain. *Arch Neurol.* 1982;11:97-100.

33. Pieniadz JM, Naeser MA. Computed tomographic scan cerebral asymmetries and morphological brain asymmetries. *Arch Neurol.* 1984;41:403-409.

34. Bear D, Schiff D, Saver J, Greenberg M, Freeman R. Quantitative analysis of cerebral asymmetries. *Arch Neurol.* 1986;43:598-603.

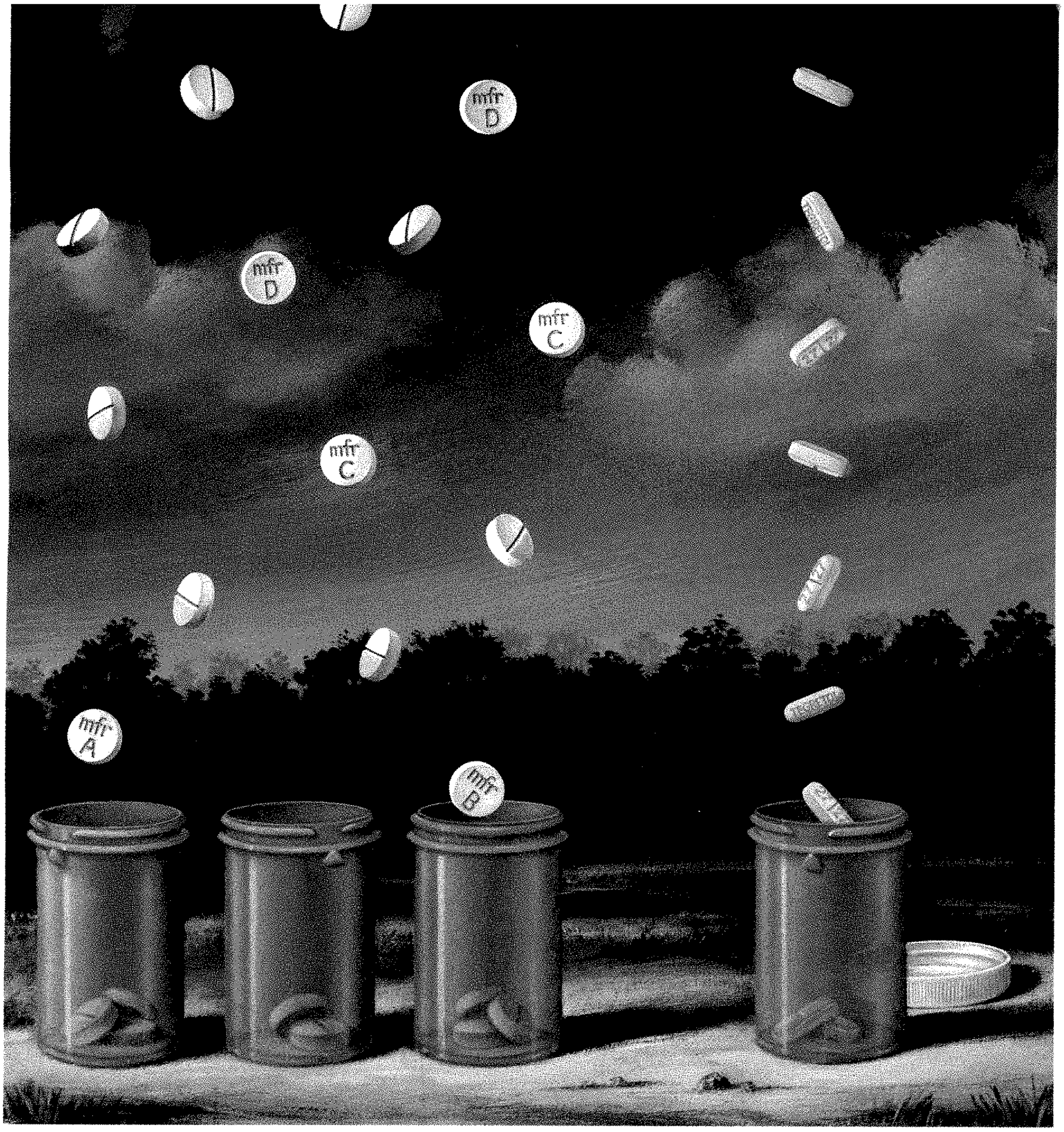
35. De Lacoste-Utamsing C, Holloway RL. Sexual dimorphism in the human corpus callosum. *Science.* 1982;216:1431-1432.

36. Bleier R, Houston L, Byne W. Can the corpus callosum predict gender, age, handedness, or cognitive differences? *Trends Neurosci.* September 1986:391-394.

37. Witelson SF. The brain connection: the corpus callosum is larger in left-handers. *Science.* 1985;229:665-668.

38. Oppenheim JS, Skerry JE, Tramo MJ, Gassaniga MS. Magnetic resonance imaging morphology of the corpus callosum in monozygotic twins. *Ann Neurol.* 1989;26:100-104.

39. De Lacoste MC, Kirkpatrick JP, Ross ED. Topography of the human corpus callosum. *J Neuropathol Exp Neurol.* 1985;44:578-591.



From refill to refill... which carbamazepine will your patient get next?

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the following page, especially the boxed warning.

CIBA–GEIGY

Prevent substitution when you prescribe Tegretol

Sign each prescription on the line that prevents substitution, or add the phrase required in your state to prevent substitution:

☐ Dispense As Written
☐ No Substitution
☐ Do Not Substitute
☐ Brand Necessary
☐ No Drug Product Selection
☐ May Not Substitute
☐ Medically Necessary

For your Medicaid patients...

To prevent substitution of TEGRETOL for your Medicaid patients, be sure to add the phrase "Brand Medically Necessary" on each prescription.

Tegretol® 200 mg scored tablets 100 mg chewable tablets
carbamazepine USP

...because there's no substitute for experience.

Tegretol® carbamazepine USP

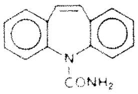
Chewable Tablets of 100 mg—red-speckled, pink **Tablets of 200 mg—pink**

> WARNING
> APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION HOWEVER. THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA
>
> ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME HOWEVER. THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS
>
> BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA. THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY NONETHELESS. COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS. THE PATIENT SHOULD BE MONITORED CLOSELY DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol carbamazepine USP is an anticonvulsant and specific analgesic for trigeminal neuralgia available as chewable tablets of 100 mg and tablets of 200 mg for oral administration Its chemical name is 5H-dibenz [b.f]azepine-5-carboxamide and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone Its molecular weight is 236 27

Inactive Ingredients Colloidal silicon dioxide FD&C Red No 3 (chewable tablets only). FD&C Red No 40 (200-mg tablets only). flavoring (chewable tablets only) gelatin. glycerin. magnesium stearate sodium starch glycolate (chewable tablets only). starch stearic acid and sucrose (chewable tablets only)

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia The mechanism of action remains unknown

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution thus avoiding undesirably high peak concentrations Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets Tegretol in blood is 76% bound to plasma proteins Plasma levels of Tegretol are variable and may range from 0 5-25 µg/ml, with no apparent relationship to the daily intake of the drug Usual adult therapeutic levels are between 4 and 12 µg/ml Following oral administration serum levels peak at 4 to 5 hours The CSF/serum ratio is 0 22 similar to the 22% unbound Tegretol in serum Because Tegretol may induce its own metabolism the half-life is also variable Initial half-life values range from 25-65 hours with 12-17 hours on repeated doses Tegretol is metabolized in the liver After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites with only 3% of unchanged Tegretol Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues with higher levels found in liver and kidney than in brain and lungs

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types

1 Partial seizures with complex symptomatology (psychomotor temporal lobe) Patients with these seizures appear to show greater improvement than those with other types
2 Generalized tonic-clonic seizures (grand mal)
3 Mixed seizure patterns which include the above or other partial or generalized seizures

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General)

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia

Beneficial results have also been reported in glossopharyngeal neuralgia

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline desipramine, imipramine, protriptyline nortriptyline, etc Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days or longer if the clinical situation permits

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with Tegretol These reactions have been extremely rare However, a few fatalities have been reported

Tegretol has shown mild anticholinergic activity; therefore patients with increased intraocular pressure should be closely observed during therapy

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE)

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac hepatic or renal damage adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease must be performed during treatment with this drug since liver damage may occur The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

Baseline and periodic eye examinations, including slit-lamp funduscopy and tonometry are recommended since many phenothiazines and related drugs have been shown to cause eye changes

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance In addition measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used

Thyroid function tests have been reported to show decreased values with Tegretol administered alone

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs

Drug Interactions: The simultaneous administration of phenobarbital phenytoin or primidone or a combination of two produces a marked lowering of serum levels of Tegretol The effect of valproic acid on Tegretol blood levels is not clearly established although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding

The half-lives of phenytoin warfarin doxycycline and theophylline were significantly shortened when administered concurrently with Tegretol Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen

Concomitant administration of Tegretol with erythromycin cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases Also concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine when administered to Sprague-Dawley rats for two years in the diet at doses of 25 75 and 250 mg/kg/day resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males

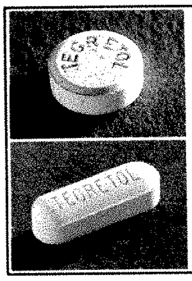
Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results The significance of these findings relative to the use of carbamazepine in humans is at present unknown

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg In rat teratology studies 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate 1; talipes, 1, anophthalmos 2) In reproduction studies in rats nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations including spina bifida Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Retrospective case reviews suggest that compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy Therefore monotherapy is recommended for pregnant women

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown

Nursing Mothers: During lactation concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration

Because of the potential for serious adverse reactions in nursing infants from carbamazepine a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system

The most frequently observed adverse reactions, particularly during the initial phases of therapy are dizziness, drowsiness unsteadiness, nausea, and vomiting To minimize the possibility of such reactions therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

Hemopoietic System Aplastic anemia agranulocytosis pancytopenia bone marrow depression thrombocytopenia leukopenia, leukocytosis, eosinophilia acute intermittent porphyria

Skin Pruritic and erythematous rashes, urticaria toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis erythema multiforme and nodosum, purpura aggravation of disseminated lupus erythematosus alopecia and diaphoresis in certain cases, discontinuation of therapy may be necessary

Cardiovascular System Congestive heart failure edema, aggravation of hypertension, hypotension syncope and collapse, aggravation of coronary artery disease arrhythmias and AV block primary thrombophlebitis recurrence of thrombophlebitis and adenopathy or lymphadenopathy

Some of these cardiovascular complications have resulted in fatalities Myocardial infarction has been associated with other tricyclic compounds

Liver Abnormalities in liver function tests cholestatic and hepatocellular jaundice, hepatitis

Respiratory System Pulmonary hypersensitivity characterized by fever dyspnea pneumonitis or pneumonia

Genitourinary System Urinary frequency acute urinary retention oliguria with elevated blood pressure, azotemia renal failure, and impotence Albuminuria glycosuria, elevated BUN and microscopic deposits in the urine have also been reported

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day Additionally rats receiving Tegretol in the diet for two years at dosage levels of 25 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis In dogs it produced a brownish discoloration presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher Relevance of these findings to humans is unknown

Nervous System Dizziness drowsiness, disturbances of coordination, confusion, headache fatigue, blurred vision, visual hallucinations transient diplopia, oculomotor disturbances, nystagmus speech disturbances abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness tinnitus, and hyperacusis

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established

Digestive System Nausea, vomiting, gastric distress and abdominal pain diarrhea, constipation anorexia and dryness of the mouth and pharynx including glossitis and stomatitis

Eyes Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported Although a direct causal relationship has not been established many phenothiazines and related drugs have been shown to cause eye changes

Musculoskeletal System Aching joints and muscles, and leg cramps

Metabolism Fever and chills Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported Cases of frank water intoxication with decreased serum sodium (hyponatremia) and confusion have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests)

Other Isolated cases of a lupus erythematosus-like syndrome have been reported There have been occasional reports of elevated levels of cholesterol HDL cholesterol and triglycerides in patients taking anticonvulsants

A case of aseptic meningitis accompanied by myoclonus and peripheral eosinophilia has been reported in a patient taking carbamazepine in combination with other medications The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose adults >60 g (39-year-old man) Highest known doses survived adults 30 g (31-year-old woman), children 10 g (6-year-old boy), small children 5 g (3-year-old girl)

Oral LD 50 in animals (mg/kg) mice, 1100-3750; rats, 3850-4025, rabbits, 1500-2680, guinea pigs, 920

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours Neuromuscular disturbances are the most prominent Cardiovascular disorders are generally milder and severe cardiac complications occur only when very high doses (>60 g) have been ingested

Respiration Irregular breathing, respiratory depression

Cardiovascular System Tachycardia, hypotension or hypertension, shock conduction disorders

Nervous System and Muscles Impairment of consciousness ranging in severity to deep coma Convulsions especially in small children Motor restlessness, muscular twitching tremor, athetoid movements opisthotonos, ataxia drowsiness, dizziness mydriasis nystagmus adiadochokinesia, ballism, psychomotor disturbances, dysmetria Initial hyperreflexia followed by hyporeflexia

Gastrointestinal Tract Nausea, vomiting

Kidneys and Bladder Anuria or oliguria, urinary retention

Laboratory Findings Isolated instances of overdosage have included leukocytosis reduced leukocyte count glycosuria and acetonuria EEG may show dysrhythmias

Combined Poisoning When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug which may be achieved by inducing vomiting irrigating the stomach, and by taking appropriate steps to diminish absorption If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital while ensuring that vital functions are safeguarded There is no specific antidote

Elimination of the Drug Induction of vomiting

Gastric lavage Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated especially if the patient has also consumed alcohol

Measures to Reduce Absorption Activated charcoal laxatives

Measures to Accelerate Elimination Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure Replacement transfusion is indicated in severe poisoning in small children

Respiratory Depression Keep the airways free; resort, if necessary, to endotracheal intubation artificial respiration, and administration of oxygen

Hypotension, Shock. Keep the patient's legs raised and administer a plasma expander If blood pressure fails to rise despite measures taken to increase plasma volume use of vasoactive substances should be considered

Convulsions Diazepam or barbiturates

Warning Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension and coma However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week)

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure body temperature pupillary reflexes and kidney and bladder function should be monitored for several days

Treatment of Blood Count Abnormalities If evidence of significant bone marrow depression develops the following recommendations are suggested (1) stop the drug (2) perform daily CBC, platelet and reticulocyte counts (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery

Special periodic studies might be helpful as follows (1) white cell and platelet antibodies (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing (4) cytogenetic studies on marrow and peripheral blood (5) bone marrow culture studies for colony-forming units (6) hemoglobin electrophoresis for A_2 and F hemoglobin and (7) serum folic acid and B_{12} levels

A fully developed aplastic anemia will require appropriate intensive monitoring and therapy, for which specialized consultation should be sought

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests) Dosage should be adjusted to the needs of the individual patient A low initial daily dosage with a gradual increase is advised As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level Tablets should be taken with meals

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b i d Increase at weekly intervals by adding up to 200 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age Doses up to 1600 mg daily have been used in adults in rare instances ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily

Children 6-12 years of age—Initial: 100 mg b i d Increase at weekly intervals by adding 100 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg ***Maintenance:*** Adjust dosage to the minimum effective level usually 400-800 mg daily

Combination Therapy: Tegretol may be used alone or with other anticonvulsants When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C)

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b i d on the first day for a total daily dose of 200 mg This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain Do not exceed 1200 mg daily

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily However, some patients may be maintained on as little as 200 mg daily while others may require as much as 1200 mg daily At least once every 3 months throughout the treatment period attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled pink single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak*—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0027-61

Samples when available are identified by the word *SAMPLE* appearing on each tablet

Protect from moisture

Dispense in tight container (USP)

Also available as Tegretol suspension 100 mg/5 ml, in 450 ml bottles

Printed in U S A C90-34 (Rev 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

Magnetic Resonance Imaging White Matter Lesions and Cognitive Impairment in Hypertensive Individuals

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• To search for a morphologic basis of cognitive impairment possibly associated with essential hypertension, we studied 35 otherwise asymptomatic hypertensive individuals (mean age, 38.7 years; range, 22 to 49 years) and 20 normotensive control subjects (mean age, 37.9 years; range, 26 to 49 years) using neuropsychologic tests and magnetic resonance imaging. Irrespective of drug treatment, hypertensive individuals performed significantly worse than did control subjects when assessed for verbal memory and total learning and memory capacity, while there were no differences in test results of visual memory, attention, vigilance, and reaction time. The hypertensive individuals also described themselves as less active but ranked similar on five other mood subscales. Punctate high-signal intensities of the white matter were found almost twice as often in the hypertensive group (38%) as in the control group (20%). There was no difference in test performance between hypertensive individuals with and those without white matter lesions, however. Our results confirm the presence of subtle neuropsychologic deficits and indicate a higher frequency of white matter signal abnormalities in essential hypertension, as shown on magnetic resonance imaging, but do not indicate a correlation of these findings with each other.

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Subtle deficits in the neuropsychologic test performance of hypertensive individuals appearing asymptomatic by standard clinical examination and interview have been reported by numerous groups.[1-6] The underlying mechanisms are still a matter of debate. "Functional" changes and/or parenchymal damage resulting from reduced cerebral perfusion have been implicated.[7-9]

The advent of magnetic resonance imaging (MRI) with its high sensitivity for tissue changes should provide the appropriate tool for testing the morphologic hypothesis.[10] So-called white matter lesions (WMLs) could represent the substrate looked for. These focal areas of high-signal intensity in the deep and subcortical white matter are an incidental finding on many MRI studies of both patients and neurologically asymptomatic individuals.[11-17] Hypertension is their main predictor besides age.[12]

Recently, Rao and coworkers[18] found no association between WML and neuropsychologic performance when examining healthy middle-aged volunteers. Subjects with hypertension were excluded from their study, however, and the authors concede that the cause and consequence of hyperintense white matter foci on MRI could be different for normotensive and hypertensive populations.

In the light of these results, we wanted to determine if hypertension-related tissue damage can be detected by MRI and cognitive impairment, if present in the group of hypertensive individuals, can be explained on the basis of these findings. To exclude other factors known to be associated with impaired cognitive performance and/or parenchymal abnormalities of the brain, we studied asymptomatic young and middle-aged individuals with essential arterial hypertension only.

SUBJECTS AND METHODS

Subjects

We studied 35 individuals (mean age, 38.7 ± 7.7 years; 26 men and nine women) suffering from essential hypertension. Attendants of a preventive medical examination program of the general regional health insurance company (Steiermärkische Gebietskrankenkasse, Graz, Austria) below 50 years of age who had had blood pressure readings greater than 160 mm Hg systolic and/or greater than 95 mm Hg diastolic at two independent visits or one reading above these limits and a history of hypertension were asked to participate in the study and were admitted to the Department of Neurology. Only those without clinical evidence of cardiovascular and/or cerebrovascular disease, diabetes mellitus, or other neurologic, psychiatric, or systemic disorders possibly associated with cognitive impairment or cerebral damage were then entered into the study. Subjects with a history of head injury and alcohol or drug abuse were not eligible for the same reasons.

In the study group the interval between the first diagnosis of hypertension and enrollment ranged from 1 to 139 months (mean, 74 months). Twenty-three subjects were treated with low-dose β-blockers (50-mg metoprolol, eight patients; 100-mg metoprolol, 10 patients; 50-mg atenolol, three patients; 100-mg celiprolol, one patient; and 5-mg carazolol, one patient). One patient received a combination of 0.4-mg dihydroergocristin mesylate, 2.5-mg clopamide, and 0.05-mg reserpine. Eleven individuals had not been taking medication for at least 1 month prior to the study.

The control group consisted of 20 volunteers (mean age, 37.9 ± 4.7 years; 13 men and seven women) from a field study on the incidence of cerebrovascular risk factors in Graz and the surrounding area, which was performed at the same time. They had to meet the same selection criteria as described for the hypertensive group, except for a negative history of hypertension and blood pressure recordings less than 140/85 mm Hg at two independent visits.

The demographic data of both groups and their blood pressure readings at the time of

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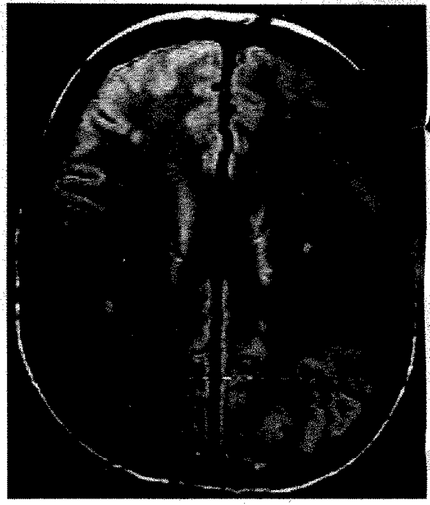
Table 1.—Demographic Data and Blood Pressure Recordings at the Time of the Study

	Hypertensive Subjects			
Demographic Data	**All (n = 35)**	**Treated (n = 24)**	**Untreated (n = 11)**	**Control Subjects (n = 20)**
Age range, y	22-49	28-49	22-49	26-49
Mean (SD) age, y	38.7 (7.7)	39.1 (7.2)	35.5 (8.8)	37.9 (4.7)
Mean (SD) education, y	9.6 (2.7)	9.4 (2.2)	10.1 (3.5)	9.8 (2.9)
Mean (SD) blood pressure, mm Hg				
Systolic	149.9 (18.6)*	147.3 (17.3)*	152.7 (14.7)*	123.5 (10.4)
Diastolic	99.4 (11.7)*	98.6 (9.79)*	101.8 (9.05)*	80.6 (2.9)

*Duncan *t* test, $P < .01$ vs control subjects.



The proton density magnetic resonance imaging sequence reveals multiple punctate hyperintense lesions in the deep and subcortical white matter of a 45-year-old hypertensive woman.

the MRI study are displayed in Table 1. All study subjects were right-handed.

Neuropsychologic Testing

We tested memory and learning abilities (Bäumler's Lern- und Gedächtnistest-LGT 3[19]), attention (d2 test[20]), vigilance and reaction time (computerized system by Quatember and Maly[21]), and mood (adjective list of Janke and Debus[22]). This battery was always administered in the same order and under the same laboratory conditions by one neuropsychologist unaware of the individual's diagnosis and MRI findings. All tests have been widely used for the assessment of normal populations in the German-language area.

Briefly, the Bäumler's Lern- und Gedächtnistest (LGT 3) is a highly demanding test for learning capacity and intermediate memory. It is a paper-pencil procedure and consists of six subtests. Three subtests (word and digit association tasks and story recall) assess verbal memory, and two subtests screen visuospatial memory (trail and design recall). The sum of weighted scores from these subtests and of an image recognition paradigm results in the total learning and memory performance score.

The d2 test is a letter identification test examining visual attention. The number of items correctly identified within 21 seconds per line is recorded. The distribution of errors among a total of 14 lines reflects attention span.

Vigilance and reaction time were determined with a computerized system developed by Quatember and Maly.[21] The individual is requested to identify changes in a sequence of light flashes, and the time needed for response is termed reaction time.

The test of Janke and Debus[22] is a self-administered questionnaire consisting of 136 adjectives describing states of activation, extro-introversion, well-being, emotional stress, and anxiety.

Magnetic Resonance Imaging

The MRI was performed with a 1.5-Tesla superconducting magnet (Gyroscan S 15, Philips, Eindhoven, the Netherlands) and the spin-echo technique. Sagittal T_1-weighted (TR/TE, 600/30 milliseconds) and axial proton density and T_2-weighted (TR/TE, 1800 to 2500/30 and 60 milliseconds) scans were obtained with a slice thickness of 5 mm. These images were reviewed for signal abnormalities and cerebral atrophy in a blinded fashion by randomly mixing the scans of control subjects and of 32 hypertensive patients (two patients were not scanned, and one set of images was excluded because of poor quality). Sulcal and ventricular enlargements were graded as not present, mild, moderate, or severe.

Statistical Analysis

Calculations were performed with the microcomputer version of the Statistical Package for Social Sciences.[23] One-way analysis of variance was employed first and the Duncan *t* test was used to ascertain significant differences between groups. Frequency distributions were compared by means of Fisher's Exact Test.

RESULTS

MRI Findings

Punctate hyperintense foci in the deep and subcortical white matter were the only signal abnormalities present on MRI scans of both groups (Figure). They were found almost twice as often in hypertensive patients as in control subjects (Table 2). The number of WMLs ranged from one to four (mean, 2.3) in normotensive individuals and from one to 19 (mean, 4.3) in hypertensive subjects. These differences did not reach statistical significance, however. Cortical and ventricular atrophies were found equally often in both groups (Table 2). The extent of atrophy was mild in most cases, except for one individual in each group with a moderate ventricular enlargement.

Neuropsychologic Testing

The hypertensive individuals performed worse than control subjects in almost all tests. Significant differences were reached with respect to the verbal memory and the total learning and memory scores ($P < .05$). This was true for both treated and untreated hypertensive subjects. An analysis for dose-dependent effects of the β-blocker most frequently used in our study group (metoprolol) revealed no significant differences in neuropsychologic performance of individuals on a 50-mg or 100-mg metoprolol regimen. Treated and untreated hypertensive subjects reported significantly lower degrees of activation (Table 3).

A comparison between hypertensive subjects with and without WML did not yield significantly different scores for any of the test items (Table 4). Analysis of potentially confounding factors in both groups revealed matching with respect to sex and length of education. Age was significantly higher in hypertensive subjects with WML (Table 4). The proportions of untreated patients (29% vs 35%) and of those receiving lipophilic (54% vs 60%) or hydrophilic (9% vs 5%) β-blockers in the samples with and without WML were comparable, with one patient with WML receiving a drug combination (8%).

COMMENT

In this study, clinically normal-appearing individuals below 50 years of age with essential arterial hypertension obtained significantly lower scores than normotensive control subjects for overall memory performance and learning capacity and on subscales assessing verbal mnemonic abilities. Our data, thus, confirm that neuropsychologic testing may reveal unexpected cognitive impairment in such hypertensive populations.[4-6]

Several reports indicate either improvement or impairment of cognitive performance from β-blockers.[24] The differences in test results observed between normotensive and hypertensive subjects in this study, however, cannot be explained on the basis of drug effects. Hypertensive subjects with and

Table 2.—Incidence of Abnormal Magnetic Resonance Imaging Findings

	Subjects, No. (%)	
	Hypertensive (n = 32)	Normotensive (n = 20)
White matter lesions	12 (38)	4 (20)
Cortical atrophy	5 (15)	5 (25)
Ventricular atrophy	3 (9)	3 (15)

Table 3.—Neuropsychologic Test Results*

	Subjects			
		Hypertensive		
	Normotensive (n = 20)	All (n = 35)	Treated (n = 24)	Untreated (n = 11)
Learning and memory test (LGT 3[19]) scores				
VSM	44.5 (10.6)	40.6 (9.4)	40.2 (7.8)	41.5 (12.3)
VM	37.7 (6.8)	31.6 (10.8)†	31.9 (12.4)†	31.1 (6.8)†
TLMP	34.9 (7.4)	28.1 (8.5)†	27.4 (8.8)†	29.6 (8.2)†
Visual attention (d2 test[20]), No. of				
Correctly identified items	442.7 (79.7)	407.2 (82.2)	410.7 (84.8)	399.9 (79.9)
Falsely identified items	25.4 (19.9)	27.0 (27.1)	29.9 (29.9)	20.7 (19.8)
Errors				
Lines 1-4	7.2 (6.9)	6.0 (6.2)	6.7 (6.9)	4.4 (4.1)
Lines 5-10	10.4 (8.1)	13.0 (14.0)	14.3 (14.8)	10.3 (12.2)
Lines 11-14	8.2 (8.2)	8.0 (8.0)	8.8 (9.8)	6.5 (6.7)
Vigilance and reaction time[21]				
WMR	4.2 (2.7)	6.3 (12.5)	4.7 (4.6)	9.7 (21.2)
RT, ms	413.1 (60.8)	437.1 (73.9)	438.9 (72.8)	433.3 (79.5)
Mood questionnaire[22] scores				
AC	20.5 (3.8)	17.8 (4.4)†	18.4 (3.6)†	16.5 (5.8)†
D	3.2 (2.9)	3.9 (3.7)	3.6 (3.9)	4.6 (3.4)
WB	14.0 (6.9)	14.6 (5.9)	14.6 (5.1)	14.6 (7.8)
ES	7.3 (5.5)	7.8 (5.0)	7.9 (5.1)	7.7 (5.1)
E/I	8.4 (2.0)	8.4 (2.0)	8.6 (1.9)	8.1 (2.5)
A	9.4 (6.7)	9.7 (5.7)	8.9 (4.8)	11.4 (7.1)

*Values are mean (SD). VSM indicates visuospatial memory; VM, verbal memory; TLMP, total learning and memory performance; WMR, wrong and missed reactions; RT, reaction time; AC, activation; D, deactivation; WB, well-being; ES, emotional stress; E/I, extro-introversion; and A, anxiety.

†Duncan *t* test, $P < .05$ (in comparison with control subjects).

Table 4.—Neuropsychologic Test Results in Hypertensive Subjects With and Without White Matter Lesions*

	White Matter Lesions		
	Present (n = 12)	Absent (n = 20)	*P*†
M/F	9/3	16/4	. . .
Age, y	43.3 (5.6)	35.8 (9.3)	.02
Education, y	9.5 (2.9)	9.4 (2.8)	NS
Learning and memory test (LGT 3[19])			
VSM	41.2 (9.2)	40.2 (11.0)	NS
VM	30.3 (7.5)	33.9 (15.3)	NS
TLMP	28.5 (9.3)	27.6 (8.3)	NS
Visual attention (d2 test[20])			
Correctly identified items	408.2 (79.7)	407.3 (97.6)	NS
Falsely identified items	21.6 (16.0)	28.4 (22.2)	NS
Vigilance and reaction time[21]			
WMR	5.2 (8.4)	4.7 (3.7)	NS
RT, ms	451.2 (77.9)	423.2 (24.7)	NS
Mood questionnaire[22]			
AC	17.5 (4.9)	18.5 (4.1)	NS
D	4.4 (4.0)	3.9 (3.6)	NS
WB	13.6 (6.4)	16.0 (5.5)	NS
ES	8.8 (4.7)	7.6 (5.5)	NS
E/I	8.4 (2.2)	8.7 (1.8)	NS
A	9.7 (5.3)	11.2 (6.2)	NS

*Values are mean (SD). NS indicates not significant; see Table 3 for explanation of other abbreviations.

†Duncan *t* test.

without medication performed equally poorly. Moreover, a major drug influence is unlikely as dosages of β-blockers in our patients were in the low range, while cognitive alterations have been noted rather with high-dose regimens. The proportion of patients receiving lipophilic β-blockers, predominantly incriminated for cognitive side effects because of their brain affinity, was small compared with that of hypertensive subjects treated with substances of the hydrophilic type. Dose dependency of neuropsychologic impairment was not noted in the most frequently used representative of the latter. A comparable length of education in hypertensive patients and control subjects excludes a distortion of our finding by this factor as well.[6]

The mood questionnaire revealed significantly lower levels of activation for hypertensive individuals than for control subjects. A negative effect on mood state and personality from the recognition of worse cognitive performance has been suggested by Shapiro et al.[25] Conversely, a reduced state of activation as present in our hypertensive patients could deteriorate test performance and might have affected cognitive testing.

To our knowledge, it is the first time that MRI was used to look for a morphologic basis of subtle neuropsychologic alterations in otherwise asymptomatic hypertensive individuals. Punctate high-signal intensity lesions in the deep and subcortical white matter were noted in more than one third of this population, and this was almost twice as often as in normotensive control subjects. Recent histopathological studies indicate atrophic perivascular demyelination and gliosis resulting from focally insufficient nutrition around small vessels[26] and/or frank lacunar white matter infarcts[27,28] as the predominant correlate of such signal abnormalities. They could, thus, be a first step toward hypertensive subcortical arteriosclerotic encephalopathy, which is frequently associated with dementia.[29] The comparison of hypertensive subjects with and without WML did not reveal a significant difference on any of the administered neuropsychologic tests, however. A mismatch of both groups with respect to sex, length of education, or type of treatment that might have caused a false-negative finding could not be substantiated. Age was significantly higher in the group of hypertensive subjects with WML. This is not unexpected as Awad et al[12] identified both age and hypertension as the most important predictors of incidental MRI hyperintensities. With respect to cognitive testing, however, the higher mean age of hypertensive subjects with WML should have rather enhanced a worse performance than masked it.

It, therefore, appears that the type of MRI lesions observed in this study cannot be implicated in the cognitive impairment noted. Moreover, white matter changes described in MRI of vascular dementia and seen in cases with pathologically proved Binswanger's disease have been reported as more extensive, sometimes involving almost the entire periventricular and deep white matter.[14,29,30]

As the frequency of atrophy was also not different between normotensive and hypertensive subjects, MRI could not provide an explanation for our neuropsychologic observations. Therefore, these data are in favor of "functional" or at least not gross structural mechanisms that deteriorate cognitive performance in hypertensives of this age group.

References

1. Wilkie F, Eisendorfer C. Intelligence and blood pressure in the aged. *Science.* 1971;172:959-962.
2. Boller F, Vrtunski B, Mack JL, Kim Y. Neuropsychological correlates of hypertension. *Arch Neurol.* 1977;34:701-705.
3. Pentz CA, Elias MF, Wood WG, Schultz NA, Dineen J. Relationship of age and hypertension to neuropsychological test performance. *Exp Aging Res.* 1979;5:351-372.
4. Franceschi M, Tancredi O, Smirne S, Mercinelli A, Canal N. Cognitive processes in hypertension. *Hypertension.* 1982;4:226-229.
5. Mazzuchi A, Mutti A, Paletti A, Ravenetti C, Novarini A, Parma M. Neuropsychological deficits in arterial hypertension. *Acta Neurol Scand.* 1986;73:619-627.
6. Elias MF, Robbins MA, Schultz NR, Streeten DHP, Elias PK. Clinical significance of cognitive performance by hypertensive patients. *Hypertension.* 1987;9:192-197.
7. Evans PH. Relation of longstanding blood-pressure levels to atherosclerosis. *Lancet.* 1965;1:516-519.
8. Fisher CM. Cerebral miliary aneurysms in hypertension. *Am J Pathol.* 1972;66:313-330.
9. Rodriguez G, Arvigo F, Marenco S, et al. Regional cerebral blood flow in essential hypertension: data evaluation by a mapping system. *Stroke.* 1987;18:13-20.
10. Brant-Zawadzki M. MR imaging of the brain. *Radiology.* 1988;166:1-10.
11. Bradley WG, Waluch V, Brant-Zawadzki M, Yadley RA, Wycoff DR. Patchy periventricular white matter lesions in the elderly: a common observation during NMR imaging. *Noninv Med Imag.* 1984;1:35-41.
12. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, I: correlations with age and cerebrovascular risk factors. *Stroke.* 1986;17:1584-1589.
13. Gerard G, Weisberg LA. MRI periventricular lesions in adults. *Neurology.* 1986;36:998-1101.
14. George AE, Leon MJ, Kalnin A, Rosner L, Goodgold A, Chase N. Leukoencephalopathy in normal and pathologic aging, II: MRI of brain lucencies. *AJNR.* 1986;7:567-570.
15. Lechner H, Schmidt R, Bertha G, Justich E, Offenbacher H, Schneider G. Nuclear magnetic resonance image white matter lesions and risk factors for stroke in normal individuals. *Stroke.* 1988;19:263-265.
16. Kertesz A, Black SE, Tokar G, Benke T, Carr T, Nicholson L. Periventricular and subcortical hyperintensities on magnetic resonance imaging. *Arch Neurol.* 1988;45:404-408.
17. Schmidt R, Fazekas F, Offenbacher H, Horner S, Bertha G, Lechner H. 1.5 T magnetic resonance imaging signal hyperintensities in asymptomatic individuals within decades of age. *Stroke.* 1989;20:156. Abstract.
18. Rao SM, Mittenberg W, Bernadin L, Haughton V, Lec GJ. Neuropsychologic test findings in subjects with leuko-araiosis. *Arch Neurol.* 1989;46:40-44.
19. Bäumler G. *Lern- und Gedächtnistest-LGT 3.* Göttingen, Federal Republic of Germany: Verlag für Psychologie; 1974.
20. Brickenkamp R, Rump G. Die Stabilität des Aufmerksamkeits-Belastungstest (Test d2) über längere Zeitabschnitte. *Diagnostica.* 1966;12:17-24.
21. Quatember R, Maly J. Neuropsychologische Untersuchungsmethoden altersspezifischer Leistungsparameter. *Wien Med Wochenschr.* 1980;21:688-692.
22. Janke WJ, Debus G. Die Eigenschaftswörterliste EWL. Göttingen, Federal Republic of Germany: Dr CJ Hogrefe, Verlag für Psychologie; 1977.
23. Norusis MJ. *SPSS/PC+ for IBM PC/XT/AT.* Chicago, Ill: Statistical Program for Social Sciences; 1986.
24. Dimsdale JE, Newton RP, Joist T. Neuropsychological side effects of β-blockers. *Arch Intern Med.* 1989;149:514-525.
25. Shapiro AP, Miller RE, King HE, Ginchereau EH, Fitzgibbon K. Behavioral consequences of mild hypertension. *Hypertension.* 1982;4:355-360.
26. Kirkpatrick JB, Hayman LA. White matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathologic basis. *Radiology.* 1987;162:509-511.
27. Braffman BH, Zimmermann RA, Trojanowski JQ, Gonates NK, Hickey WF, Schlaepfer WW. Brain MRI: pathologic correlation with gross and histopathology, II: hyperintense white matter foci in the elderly. *AJNR.* 1987;9:629-636.
28. Marshall VG, Bradley WG, Marshall CE, Bhoopat T, Rhodes RH. Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology.* 1988;167:517-522.
29. Kinkel WR, Jacobs L, Polachini I, Bates V, Heffner RR. Subcortical arteriosclerotic encephalopathy (Binswanger's disease). *Arch Neurol.* 1985;42:951-959.
30. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmermann RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJNR.* 1987;8:421-426.

Visual Art in the Neurologic Career of Jean-Martin Charcot

Christopher G. Goetz, MD

• Jean-Martin Charcot, the world's first chaired professor of neurology, incorporated visual art into his daily practice of neurology. Art served as scientific documentation and was a pivotal tool in the development and dissemination of Charcot's clinicoanatomic method. Although Charcot drew extensively in clinical and laboratory studies, very few of these visual documents have ever been published or are currently available for public study. Charcot was central to the incorporation of medical photographs into the study of neurologic disease and relied heavily on visual material in his capacity as an international teacher. Art also misguided Charcot's career when he relied heavily on artwork in his attempt to convince critics that disorders seen at the Salpêtrière Hospital, Paris, France, were independent of his suggestive influence.

(*Arch Neurol.* 1991;48:421-425)

As a physician at the Salpêtrière Hospital, Paris, France, and the world's first chaired professor of neurology, Jean-Martin Charcot considered art and science to be pivotally complementary in his effort to describe and categorize neurologic disease. Science nourished art as Charcot used his own patients as models in his neurologic sketches and photographs; art nourished neurology as Charcot used art objects from past ages to convince critics that certain of the disorders he sometimes described were neither new nor of his own creation. Charcot's incorporation of art into neurology guided and misguided his individual career and established a visual tradition in neurologic study that persists today, although in new technologic forms.

ART AS SCIENTIFIC DOCUMENTATION

Charcot's dual devotion to art and science was reportedly lifelong, and he had wrestled between medicine and art as careers.[1] Charcot finally chose medicine and enrolled in the national medical school in Paris in 1842. There is almost no documentation of his student years, and his first known medical drawings date from when Charcot came to the Salpêtrière as a junior faculty member. Almost none of Charcot's clinical drawings have ever been published, and they are not available for public viewing.

After arriving at the Salpêtrière, Charcot's first task was to examine and categorize the thousands of patients haphazardly housed together throughout the walled hospital village of the Salpêtrière. With his colleague, Vulpian, Charcot gathered a massive clinical database of neurologic and geriatric diseases. This material became the core of Charcot's clinicoanatomic method, the hallmark of his Salpêtrière school.[2]

The two-step clinicoanatomic method involved artistic documentation in both phases. The first step focused on clinical description of neurologic disease, and Charcot's patient drawings documented the static deformities of chronic cases as well as evolving signs of acute illnesses. Whereas the notes accompanying the drawings were often long-winded, the drawings rapidly communicated a patient's changing neurologic state (Fig 1). Using art, Charcot documented unusual cases of dramatic amputees, pockmarked victims, and contracted hemiplegics as well as more typical cases of vascular and neurodegenerative diseases (Fig 2).

The second step of the clinicoanatomic method, which focused on anatomic and microscopic analyses, occurred after the patient died. Here, too, Charcot used his artistic skills and later engaged professional artists. He traced lesions throughout the neuraxis and documented vascular anomalies in detail (Fig 3). His early drawings were among the first to document the microscopic changes of multiple sclerosis and the spinal changes of amyotrophic lateral sclerosis (Fig 4).

Charcot's self-appointed charge was to be an objective observer, articulate and clear, independent of preconceived prejudice or expectation.[3] His personal artistic preferences focused primarily on the Dutch masters, whose realism revealed the world with simplicity and unadorned clarity.[4] His own personal artistic style reflected his scientific approach to clinical neurology. His most distinguishing clinical characteristic was a keen ability to see the essential features of diseases, culling them from among the confusion of detail. He likewise sketched with an economy of line that permitted viewers to grasp essential features at a glance. Whereas his artworks showed little artistic refinement, they were effective documents of immediate visual impact. He drew patients wherever he

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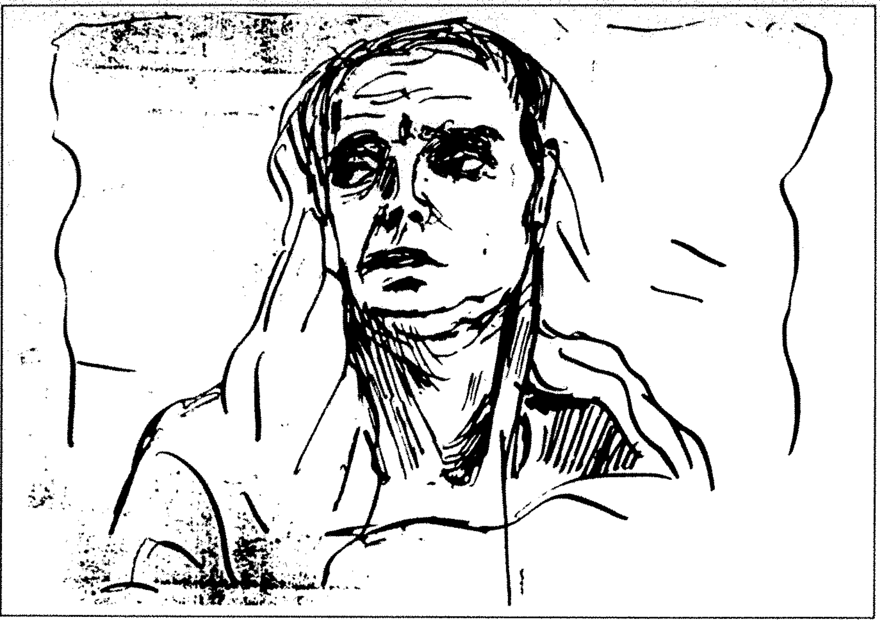

Fig 1.—A drawing from a series of sketches in the hospital record of a patient with a cerebrovascular accident, stressing here the head and eye deviation with prominence of the sternocleidomastoid muscle (original drawing in Bibliothèque Charcot, Salpêtrière Hospital, Paris, France).

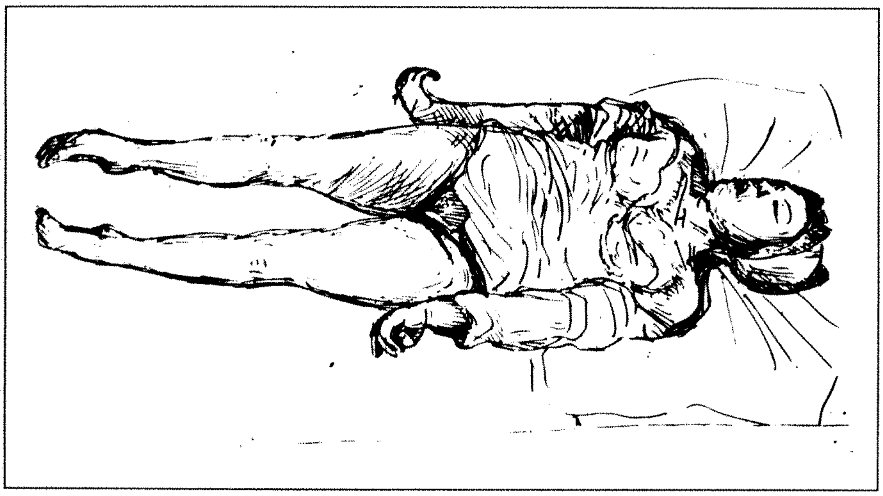

Fig 2.—Patient with decerebrate rigidity (original drawing in Bibliothèque Charcot, Salpêtrière Hospital, Paris, France).

saw them, and even when he was on vacation or on foreign travel, neurologic disease did not escape his eyes. For example, he sketched a North African with Parkinson's disease, capturing in his hasty strokes the hand posture, body attitude, joint deformities, and masked facies typical of the disease (Fig 5).

CHARCOT AND PHOTOGRAPHY

Charcot's artistic interests were undoubtedly at the core of his immediate appreciation of the new art of photography. Under his direction, a photographic service at the Salpêtrière was established by Londe,[5] and patients were regularly photographed as part of their neurologic evaluation. Whereas those with static findings were photographed only once or twice at different angles, the photographers became increasingly adept at documenting dynamic disorders with sequential and time-lapse photography methods (Fig 6). Charcot even spoke of himself in photographic terms: "I only observe, nothing more," and "I am a photographer."[6]

The Salpêtrière photographs were printed on positive silver plates, and several thousands of them were generated during Charcot's career. Some of these and many more from the period after Charcot's death are today housed in the Countway Medical Library, Boston, Mass. Such pictorial documents formed the foundation of two of Charcot's major neurologic enterprises, the *Iconographie Photographique* and the *Nouvelle Iconographie de la Salpêtrière*. The former was a limited edition of hand-pasted photographs documenting the various disorders, primarily epilepsy and hysteria, seen in the Charcot service. The latter replaced this set with a larger circulation journal with neurologic articles based specifically on photographic or artistic documentation. In the introduction of the first volume of the *Nouvelle Iconographie de la Salpêtrière*, the editors wrote:

> When a patient demonstrates signs of particular interest—various atrophies, contractures, special postures or deformities—he is immediately drawn or photographed. With the aid of this immediate record, we are able to freeze the abnormality, to decompose the various abnormal movements one by one, and thereby capture the disorder with precision. These vignettes from the Salpêtrière complement the clinical examination to form a collection of great significance.[7]

Contemporary journals based on photography or videotape (eg, *Movement Disorders*) are modern descendants of this Charcot tradition.

ART AND TEACHING

The incorporation of an artistic effort in the Charcot service had important consequences not directly linked to scientific documentation. Visual material, by nature, extends beyond language barriers and bypasses technical medical terminology. It can attract attention and provoke inquiry that might be passed over in a dry account of written neurologic description. When Charcot started his faculty career, he was acutely aware that the Salpêtrière was considered far from central Paris and that it carried the stigma of an academic wasteland, "an exile in a lost land where the pathologists and clinician had very little to see."[8] To attract students, Charcot compiled a series of rehearsed-to-perfection lessons on selected medical topics. He incorporated all his resources in these efforts, and each year their appeal grew wider. His drawings, charts, and theoretical constructs were presented in multicolored spectacle. Fifteen years before the better known aphasia diagrams of Lichteim were created, Charcot presented his audience with an elaborate series of drawings involving a bell as the central theme (Fig 7). Charcot was among the first teachers to use slide projec-

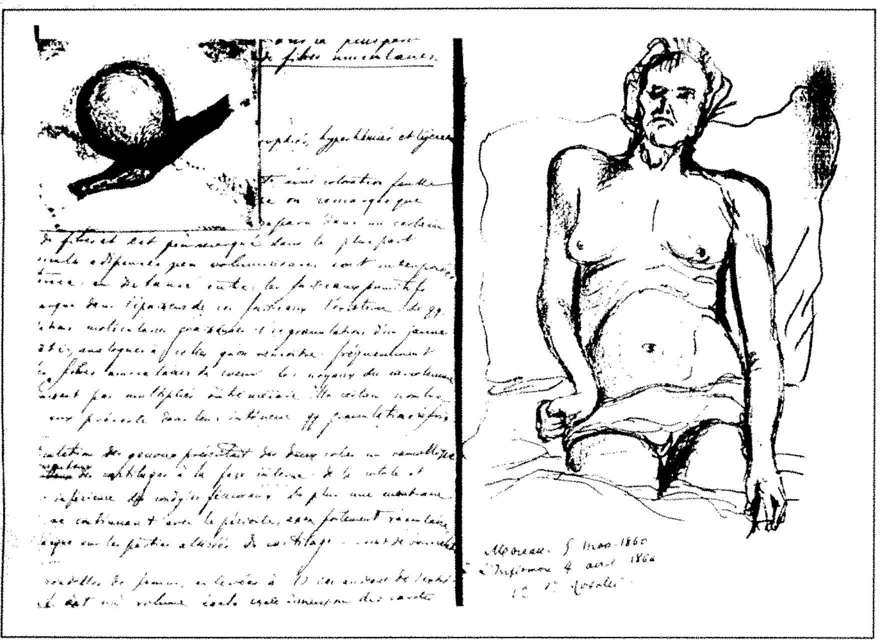

Fig 3.—Charcot's autopsy diagram of an aneurysm, drawn in red and black, and accompanying clinical notes and medical drawings of the patient (original drawing in Bibliothèque Charcot, Salpêtrière Hospital, Paris, France).

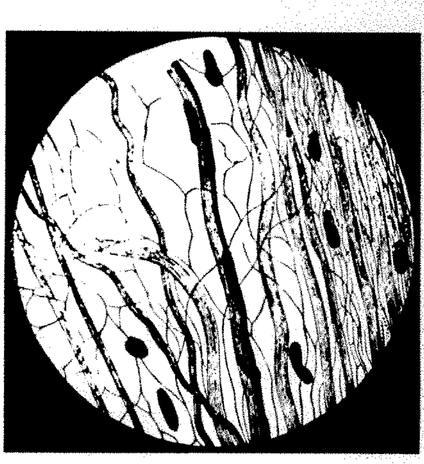

Fig 4.—Denuded axons and maintained neurons in multiple sclerosis. Drawn by Charcot and published in his *Oeuvres Complètes*.

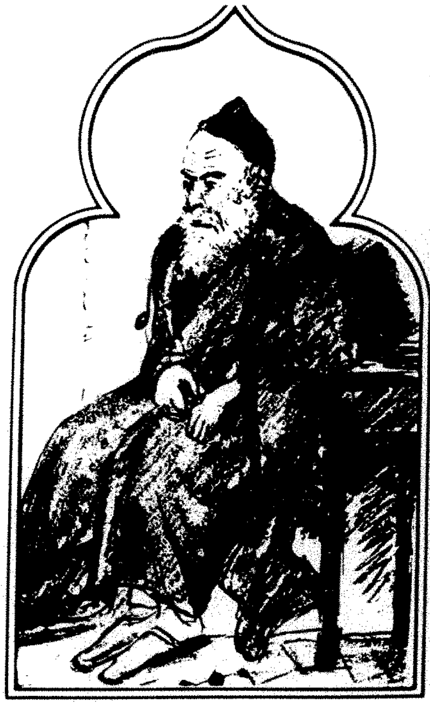

Fig 5.—A drawing by Charcot of a Moroccan with Parkinson's disease (1889). "I have seen such patients everywhere, in Rome, Amsterdam, Spain, always the same picture."[3]

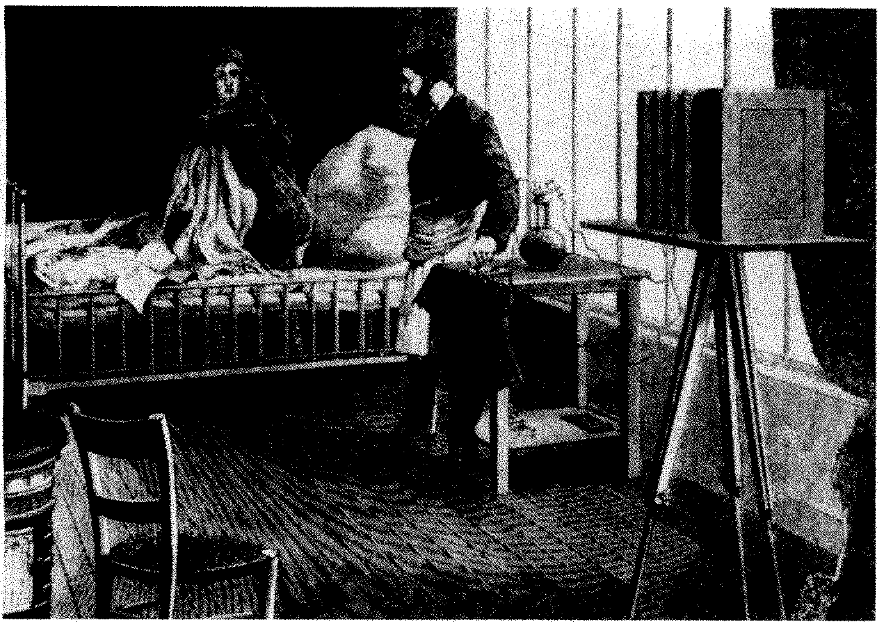

Fig 6.—Londe[5] photographing a patient in her room at the Salpêtrière Hospital, Paris, France. The photographic service was a regular part of the neurologic evaluation and research effort under Charcot's direction (from *La Nature*, No. 536; Paris, France: Bureaux du Progrès Médical; 1892.

tors in his classroom. He brought statues, photographs, and patients themselves as visual documents. He also was an excellent mime and recreated clinical syndromes for his audience, including gait abnormalities, parkinsonism, tic disorders, and various types of weakness.[2]

Charcot's reputation of magnetic presentations extended beyond the Paris medical system to the foreign medical world and to nonmedical Paris society. Especially in the 1880s and in his last years, Charcot's classroom was a mélange of doctors from eastern and western Europe and the Americas, as well as Parisian artists, journalists, politicians, and social commentators. For many of these people, whose familiarity with French or with medicine was weak, the visual material was undoubtedly pivotal to effective communication. As the American Alan Starr recalled when he first saw Charcot in a classroom:

> But grant that it was theatrical; it left on the mind of the student a series of mental pictures of patients and of lessons which no amount of private study could possibly produce. It taught man so that they could not fail to remember; and what higher result can a teacher wish?[9]

Clearly Charcot was not the first or the only investigator to use medical illustration and visual arts as a means of medical documentation. His con-

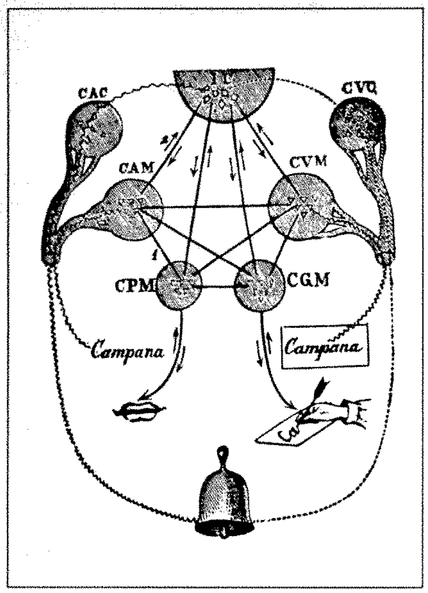

Fig 7.—Diagram of a bell used by Charcot in his presentations on aphasia. IC indicates center for ideas; CAC, auditory center; CVC, visual center; CAM, auditory center for words; CVM, visual center for words; CPM, phonetic center for words; and CGM, graphic center for words.[17]

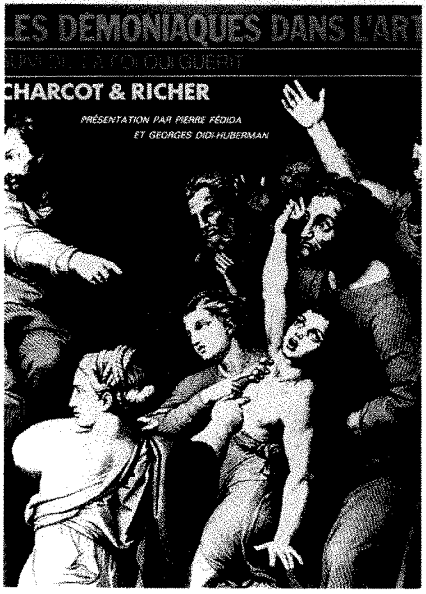

Fig 8.—Cover from Charcot's and Richer's *Demonics in Art,* showing one of the drawings used by the authors to support their thesis that hysterical epileptic fits were not a new disorder nor were they behaviors found only, or predominantly, at the Salpêtrière Hospital, Paris, France.

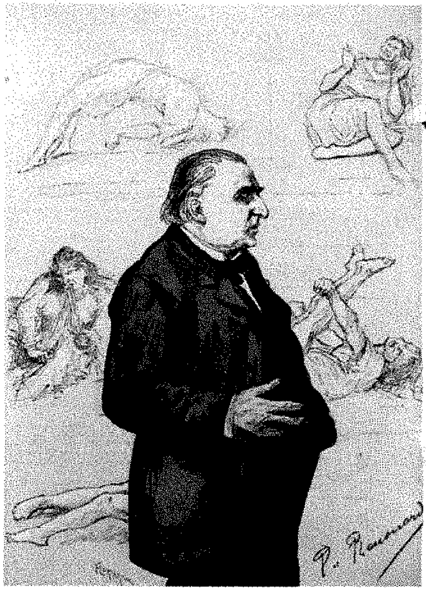

Fig 10.—Charcot and his patients. This picture was on the cover of the Paris tabloid *Revue Illustrée* and shows the extent to which Charcot became a popularized figure in nonmedical society (from Countway Medical Library, Harvard University, Boston, Mass).

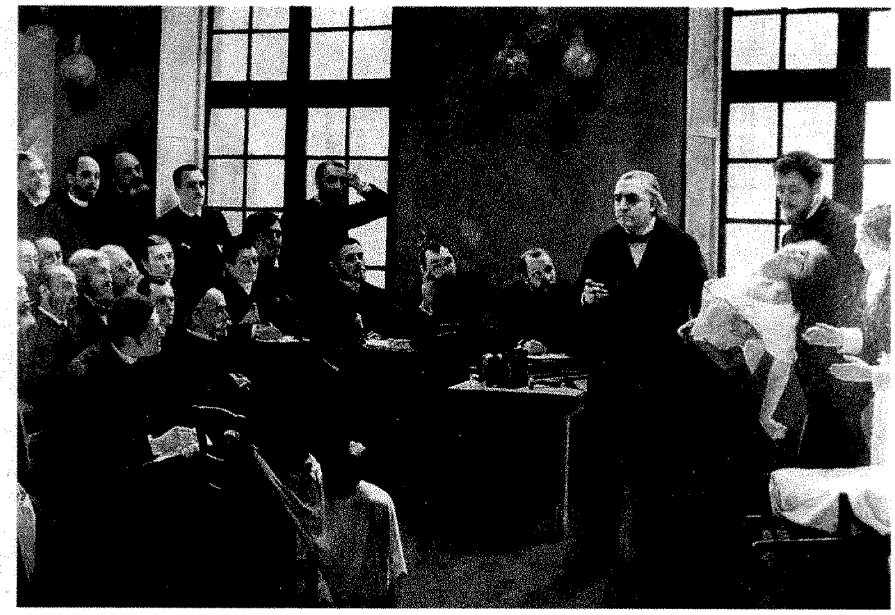

Fig 9.—A clinical lesson at the Salpêtrière Hospital, Paris, France, by Brouillet, prepared for the 1887 Paris Salon and showing Charcot, Babinski, Marie, Tourette, and other physicians, as well as artists, social commentators, and government officials in attendance.

temporaries Gowers and Hughlings Jackson included their own medical drawings in their text. Charcot, however, used visual arts in every aspect of his daily work effort. Art at the Salpêtrière was inseparable from the scientific effort and was as much the embodiment of the clinicoanatomic method as any other neurologic activity under Charcot's direction.

ART AS SCIENTIFIC JUSTIFICATION

In the sphere of organic neurology, Charcot's clinicoanatomic method met with repeated successes and established him and his school as the international pillars of clinical neurology. In the 1870s and thereafter, however, he increasingly devoted his attention to hysteria, a topic that had haunted and befuddled physicians before him.[10,11] In working with hysteria and attempting to apply the clinicoanatomic method to a condition with an elusive lesion, Charcot drifted in the eyes of his contemporaries. Visiting physicians did not recognize the spells he demonstrated in the amphitheater of the Salpêtrière, and, because the spells were too dramatic to be missed if they actually existed elsewhere, critics contended that they must be feigned or created by Charcot's own powerful suggestion. Charcot was keenly aware that hysteroepilepsy became derisively known as the Salpêtrière illness.[6]

To address this criticism and rescue his compromised scientific reputation, Charcot called on art in a way he had never previously used it. While lecturing to his students that hysteria "must henceforth become a household word,"[12] he looked to art to demonstrate that the behaviors he saw were independent of him. He went outside the Salpêtrière, beyond medicine, and indeed out of the time constraints of his own era to justify his stand that the signs of hysteria were implicit to the disease and not to the observer. At a time when he relegated much of his publication material to students, he embarked on two major works on neurologic disease in art, *The Disease and Deformed in Art* and *The Demonics in Art,* both largely focusing on hysteria (Fig 8). These works were pointedly aimed at repudiating suspicions of manipulation of falsification of clinical medicine.

In them, Charcot demonstrated that behaviors similar to those seen at the Salpêtrière could be found in medieval and mannerist paintings and other artworks depicting demonic possession or spiritual ecstacy. Charcot, however, did not succeed in accomplishing his goal, and he did not convince scientific skeptics that his personality was not intimately connected to the behaviors seen at the Salpêtrière.[13] In fact, Charcot's mere reliance on religious art that was doubtfully conceived or executed with objectivity as its guiding force and the glaring lack of historical or genre painting to support his thesis suggest a certain intellectual desperation in a man otherwise so perceptually acute. In the end, Charcot apparently recognized that his efforts had failed. The last night he worked on scientific material before he died, he reportedly told Guinon[14]: "Our conception of hysteria has become obsolete. A total revamping of this area of neurologic disease is required."

ART AS SOCIAL VEHICLE

In spite of his failure to justify scientific credibility through art, Charcot's artistic projects were of significant personal and social benefit. With them, he effectively presented himself as a multitalented and culturally sophisticated man. The importance of this dimension to his career should not be underestimated, for Charcot came from very humble origins. If a certain underlying cultural insecurity existed, his extensive literary references to poetry and Shakespeare and his artistic allusions that spanned the centuries of western culture obviously helped Charcot to present himself as a man of Renaissance dimension.[2,15] He also posed as the focal point for an immense group portrait by Brouillet, "A Clinical Lesson at the Salpêtrière" (Fig 9), a painting that became part of the celebrated 1887 Paris Salon, the focal point of artistic Paris at the time.[16] His name was known to the public, and he was even pictured on the cover of a popular street tabloid surrounded by his patients (Fig 10). These documents demonstrate that by the close of his career, Charcot, the Salpêtrière, and neurology had entered into the current social consciousness of the time. In these ways, art served Charcot directly to broaden his image and to solidify him as a cultural as well as a scientific figure of French society in the glittering close of the 19th century. Without this dimension and the close political ties that Charcot cultivated with Gambetta and other governmental figures of the third French Republic, one could question whether the original chair of neurologic diseases would ever have been established as early as 1882, and specifically in Paris at the Salpêtrière.

CHARCOT'S NEUROLOGIC ARTISTIC LEGACY

In 1893, when Charcot died, the Salpêtrière service included artists, sculptors, photographers, and a team of young neurologists well versed in visual documentation. Thereafter, the photographic wing actively continued for several generations, and the *Nouvelle Iconographie de la Salpêtrière* was published until 1929. In the 1950s, however, the Charcot Museum, with its extensive documentation of the Salpêtrière visual effort, was dissolved and the collection was lost or dispersed.[2] A pivotal investment in visual medical documentation is no longer specifically linked to the Salpêtrière, nor has it been for the past 70 years, and more recent international generations have developed innovative applications of scanning devices, videotaping, and other technologies that continue Charcot's tradition of visual neurologic documentation. These techniques are pivotal to the continued application of the clinicoanatomic neurologic method and to the refinement of modern neurologic nosology. As the centenary of Charcot's death approaches and the neurologic world invests increasingly in reexamining his written legacy, the "visual Charcot" deserves emphasis because it coalesces neurologist, teacher, social figure, and private citizen without needed grammatical translation or language study.

References

1. Guillain C; Bailey P, trans. *J. M. Charcot: His Life—His Work.* New York, NY: Hoeber; 1959.
2. Goetz CG. *Charcot: The Clinician—The Tuesday Lessons.* New York, NY: Raven Press; 1987.
3. Charcot JM. *Leçons du Mardi, 1887-88.* Paris, France: Bureaux du Progrès Médical; January 31, 1888.
4. Meige H. Charcot—artiste. *Nouv Iconogr Salpetriere.* 1898;2:489-516.
5. Londe A. *Le service photographique de la Salpêtrière.* Paris, France: Doin; 1892.
6. Charcot JM. *Leçons du Mardi, 1887-88.* Paris, France: Bureaux du Progrès Médical; February 7, 1888.
7. Richer P, Tourette G, Londe A. Advertissement. *Nouv Iconogr Salpêtrière.* 1888;1:i-ii.
8. Raymond F. Leçon d'ouverture. *Prog Med.* 1894;20:399-407.
9. Starr A. Charcot. In: *The Physician Throughout the Ages.* New York, NY: Capehart-Brown; 1928:559-562.
10. Trillat E. *Histoire de l'hystérie.* Paris, France: Seghers; 1986.
11. Laseque C. *Etudes médicales.* Paris, France: Asselin; 1884.
12. Charcot JM. *Leçons du Mardi, 1887-88.* Paris, France: Bureaux du Progrès Médical; October 30, 1888.
13. Gowers WR. *Epilepsy and Other Chronic Convulsive Disorders.* London, England: Churchill; 1881.
14. Guinon G. Charcot intime. *Paris Med.* 1925;26:511-526.
15. Goetz CG. Shakespeare in Charcot's neurologic teaching. *Arch Neurol.* 1988;45:920-921.
16. Signoret JL. Une leçon clinique à la Salpêtrière (1887) par André Brouillet. *Rev Neurol (Paris).* 1983;139:687-701.
17. Charcot JM. *Differenti forme d'afasia.* Milan, Italy: Casa Editrice Dottore F. Vallardi; 1884.

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Observations

Internal Capsule Plaque and Tonic Spasms in Multiple Sclerosis

Davide Maimone, MD; Anthony T. Reder, MD; Francesco Finocchiaro, MD; Egidio Recupero, MD

• A patient developed hemilateral tonic spasms associated with a relapse of multiple sclerosis. An area of demyelination in the right internal capsule was observed on a magnetic resonance imaging scan. This lesion was not detectable on a second magnetic resonance imaging scan 10 months after the spasms had ceased. Paroxysmal symptoms in multiple sclerosis may represent transient phenomena related to inflammation in acute plaques.

(*Arch Neurol.* 1991;48:427-429)

Paroxysmal symptoms in multiple sclerosis (MS) include trigeminal neuralgia; dysarthria; ataxia; tonic spasms, or "paroxysmal dystonia"; akinesia; and painful paresthesias.[1] These transient disturbances are sometimes the initial manifestation of the disease and usually disappear after several weeks.[2]

It has been postulated that the causative lesions are strategically localized in the spinal cord or brain stem.[3,4] However, plaques in the contralateral hemispheric white matter can also be associated with tonic spasms.[5,6]

We describe a young woman with definite MS[7] who developed unilateral tonic spasms associated with a plaque in the contralateral internal capsule. After the attacks resolved, the lesion was no longer evident on magnetic resonance imaging (MRI) scan, showing that tonic spasms in MS may result from plaques located above the brain stem. Paroxysmal symptoms in MS are more likely to occur during active demyelination and may be secondary to axonal irritation by lymphokines.

REPORT OF A CASE

A 26-year-old woman was admitted with a 10-day history of tonic spasms. These were characterized by tonic flexion of the left elbow and wrist and extension of the fingers at the metacarpophalangeal and proximal interphalangeal joints. The left leg was extended with plantar flexion and moderate intrarotation of the foot. Left facial grimacing was often present, as well as a sense of painful discomfort. These spasms were not associated with aura, loss of consciousness, tonic clonic movements, loss of sphincter control, or postictal phenomena. The attacks were mostly spontaneous, lasted 15 to 30 seconds, and occurred 20 to 30 times a day. They could be occasionally elicited by sustained extension of the arms or by sudden emotions.

Three weeks earlier, the patient had experienced dizziness and mild left hemiparesis, with ipsilateral numbness and paresthesias. The diagnosis was possible MS, and the patient was treated with cosyntropin. After 7 days she was discharged in remission, but developed the paroxysms 7 days later.

On admission, she had a mild left hemiparesis and left central facial paresis, right internuclear ophthalmoplegia, and slight impairment of vibratory sensation in the left limbs. Her left knee reflex was moderately brisk and left abdominal reflexes were absent, but plantar responses were normal on both sides. Carbamazepine, 200 mg twice a day, aborted the crises in 2 days.

The complete blood cell count, erythrocyte sedimentation rate, blood chemistry values, antinuclear antibody titer, complement levels, and serum immunoglobulin values were normal. The cerebrospinal fluid had seven nucleated cells per cubic millimeter, an elevated IgG index (0.97; normal, <0.7), increased intrathecal IgG synthesis rate (6.7 mg/d; normal, <3.3 mg/d), and oligoclonal bands.

Repeated electroencephalographic recordings during the attacks and interictally were normal. The visual evoked potentials, brain-stem auditory evoked potentials, and somatosensory evoked potentials were within normal ranges. The computed tomographic scan did not show any low-density or enhancing white matter lesions or other focal lesions.

The MRI study was performed on a 0.5-T system. On T_2-weighted images, an area of increased signal was located in the posterior limb of the right internal capsule (Fig 1).

Ten months later, the patient experienced a new episode of right-sided weakness and tingling and unsteadiness of gait. She had a mild right hemiparesis with brisk deep tendon reflexes bilaterally, a right extensor plantar response, horizontal nystagmus, and decreased vibratory sensation in the distal lower limbs. No abnormal movements or other paroxysmal symptoms occurred.

On MRI, new foci of increased T_2 signal appeared in the periventricular white matter and the left internal capsule (Fig 2). The previous lesion in the internal capsule of the right hemisphere was no longer evident.

Another cosyntropin treatment was given, and the patient was discharged in remission after 2 weeks of therapy.

COMMENT

Tonic spasms, also known as tonic seizures or paroxysmal dystonia, are sudden attacks of abnormal involuntary postures of one or more limbs, and often resemble tetanic spasms.[8] They can be associated with facial grimacing and painful sensations that localize to the same areas as the motor symptoms. Their distribution is

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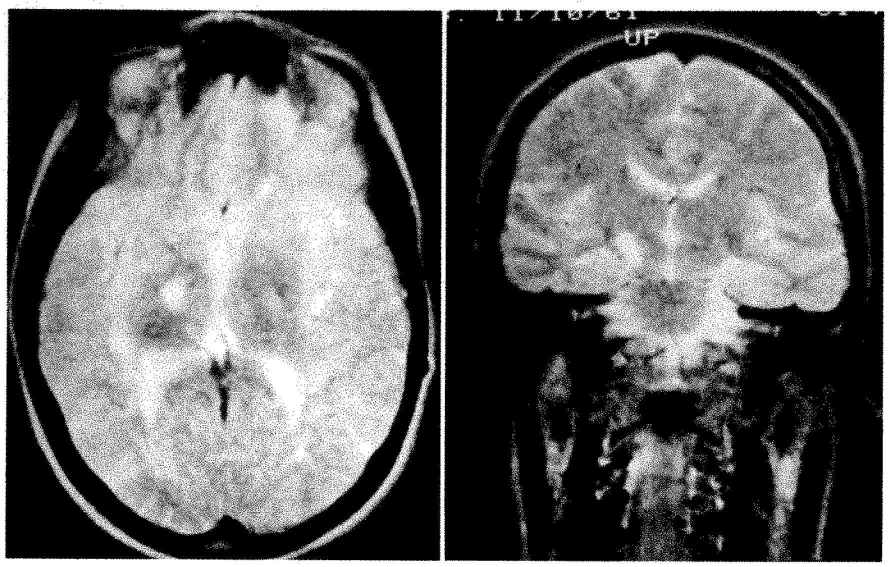

Fig 1.—Axial (left) and coronal (right) slices from the first magnetic resonance imaging scan, demonstrating a lesion in the right internal capsule.

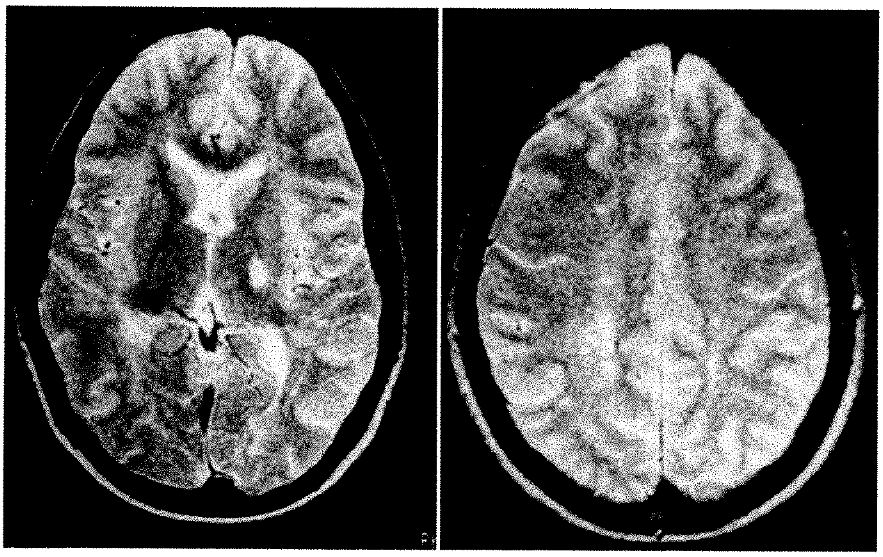

Fig 2.—Axial slice(s) from the second magnetic resonance imaging scan, showing a lesion in the left internal capsule (left) and multiple bilateral foci of demyelination in the centrum semiovale (right). Note that the lesion observed in the first scan has disappeared.

mainly unilateral, although contralateral spreading and bilateral attacks have also been reported.[4,9] Autonomic symptoms may occur, and include piloerection, perspiration, and skin flushing.[4,9] Tonic spasms are usually spontaneous, but can be evoked by active or passive movements,[4,8,10] sensory stimuli,[4,8,10] hyperventilation,[4,10,11] or emotions. The spasms last for only 30 seconds to 2 minutes, but they occur at high frequencies, ranging from 10 to 30 times a day. Almost invariably the spasms subside after weeks or months without treatment. Some antiepileptic drugs (eg, carbamazepine) suppress the attacks within a few days.[11]

Although tonic spasms may occur in various neurologic disorders,[12] they are most commonly associated with MS. Before computerized imaging techniques, it was postulated that tonic spasms were caused by MS plaques in the brain stem or the spinal cord.[5,6] More recently, hemilateral tonic spasms in two patients with MS were associated with lesions in the contralateral internal capsule on computed tomographic or MRI scans.[3,4] In our patient, the association of left-sided tonic spasms with a plaque in the right internal capsule seems more than fortuitous. The internal capsule lesion was the sole area of demyelination detected on MRI when the paroxysms occurred. Furthermore, the solitary plaque was located above the brain stem, providing an anatomical explanation for the clinical signs of contralateral spasms and facial grimacing.

Paroxysmal symptoms in MS, particularly tonic spasms, have been proposed to have an epileptic origin[8,10] because of their therapeutic response to antiepileptic drugs and their similarity to some forms of reflex epilepsy. A cortical localization, however, appears unlikely because there is no alteration of consciousness, even when tonic spasms spread bilaterally, and because there is a total lack of paroxysmal activity on the electroencephalogram. For these reasons, tonic spasms would be more likely to originate at subcortical, mesencephalic, or spinal levels.[3,4,8-10]

Demyelination causes axons to be hypersensitive to minor insults.[11] Paroxysms could then be triggered by reduction of ionized calcium after hyperventilation[8] or by ephaptic activation of axons in plaques.[1] Demyelination of afferent inhibitory pathways might also contribute to the pathologic discharges.[1]

In addition, inflammatory irritation could provoke paroxysmal symptoms.[9] Active lesions in MS are characterized by lymphocytic infiltrates and in situ secretion of lymphokines and interferons.[13,14] Leukocyte interferon and interleukin 2 enhance excitability of neurons.[15-17] Soluble factors released during inflammation could excite demyelinated axons in MS plaques.

In our case, as in most reported cases, the paroxysms were associated with other signs of exacerbation. The disappearance of the MRI lesion corresponded with the remission of symptoms. Changes in MRI plaques can develop over time in relapsing-remitting MS and tend to parallel the clinical activity of the disease.[18,19] The reported duration of several weeks for these transient plaques is temporally consistent with the natural course of paroxysms in MS.[2,19] Hyperactivity of the immune system occurs during MS exacerbations,[20,21] and inflammatory infiltrates are found in active plaques.[22] We suggest that paroxysmal symptoms in MS may sometimes originate from axonal irritation secondary to release of excitatory lymphokines.

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References

1. Osterman PO, Westerberg CE. Paroxysmal attacks in multiple sclerosis. *Brain.* 1975;98:189-202.
2. Berger JR, Sheremata WA, Melamed E. Paroxysmal dystonia as the initial manifestation of multiple sclerosis. *Arch Neurol.* 1984;41:747-750.
3. Castaigne P, Cambier J, Masson M, et al. Les manifestations motrices paroxystiques de la sclerose en plaque. *Presse Med.* 1970;40:1921-1924.
4. Shibasaki H, Kuroiwa Y. Painful tonic seizure in multiple sclerosis. *Arch Neurol.* 1974;30:47-51.
5. Watson CP, Chiu M. Painful tonic seizures in multiple sclerosis: localization of a lesion. *Can J Neurol Sci.* 1979;6:359-361.
6. Honig LS, Wasserstein PH, Adornato BT. The anatomic basis of tonic spasms in multiple sclerosis. *Neurology.* 1988;38(suppl 1):236.
7. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983;13:227-231.
8. Matthews WB. Tonic seizures in multiple sclerosis. *Brain.* 1958;81:193-206.
9. Kuroiwa Y, Araki S. Lhermitte's sign and reflex tonic spasm in demyelinating diseases with special reference to their localizing value. *Kyushu J Med Sci.* 1963;14:29-38.
10. Kreindler A, Carda M, Petresco AR, Botes MI. Considerations sur l'étiopathogènie des crises toniques dans l'encéphalomyélite disséminée. *Rev Neurol (Paris).* 1962;107:353-369.
11. Espir MLE, Millac P. Treatment of paroxysmal disorders in multiple sclerosis with carbamazepine. *J Neurol Neurosurg Psychiatry.* 1970;33:528-531.
12. Lance JW. Sporadic and familial varieties of tonic seizures. *J Neurol Neurosurg Psychiatry.* 1963;26:51-59.
13. Traugott U, Lebon P. Multiple sclerosis: involvement of interferons in lesion pathogenesis. *Ann Neurol.* 1988;24:243-251.
14. Hofman FM. Cytokines in central nervous system disease. In: Goetzl EJ, Spector NH, eds. *Neuroimmune Networks: Physiology and Diseases.* New York, NY: Alan R Liss Inc; 1989:65-71.
15. Calvet MC, Gresser I. Interferon enhances the excitability of cultured neurons. *Nature.* 1979;278:558-560.
16. Dafny N, Prieto-Gomez B, Reyes-Vazquez C. Does the immune system communicate with the central nervous system? interferon modifies central nervous activity. *J Neuroimmunol.* 1985;9:1-12.
17. Bindoni M, Perciavalle V, Berretta S, Belluardo N, Diamantstein T. Interleukin 2 modifies the bioelectric activity of some neurosecretory nuclei in the rat hypothalamus. *Brain Res.* 1988;462:10-14.
18. Uhlenbrock D, Seidel D, Gehlen W, et al. MR imaging in multiple sclerosis: comparison with clinical, CSF, and visual evoked potential findings. *AJNR.* 1988;9:59-67.
19. Isaac C, Li DKB, Genton M, et al. Multiple sclerosis: a serial study using MRI in relapsing patients. *Neurology.* 1988;38:1511-1515.
20. Reder AT, Arnason BGW. Immunology of multiple sclerosis. In: Vinken PJ, Bruyn GW, Klawans HL, eds. *Handbook of Clinical Neurology: Demyelinating Diseases.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1985:337-395.
21. Oger J, Kastrukoff LF, Li DKB, Paty DW. Multiple sclerosis: in relapsing patients, immune functions vary with disease activity as assessed by MRI. *Neurology.* 1988;38:1739-1744.
22. Traugott U, Reinherz EL, Raine CS. Multiple sclerosis: distribution of T cells, T cell subsets and Ia-positive macrophages in lesions of different ages. *J Neuroimmunol.* 1983;13:227-231.

Hypothalamic or Central Obesity Is Associated With an Early Rise in Plasma Insulin Concentration

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• Insulin levels in a 7-year-old boy with hyperphagia and obesity following an episode of meningoencephalitis were studied sequentially during the course of progressive weight gain. High fasting insulin levels (1183 pmol/L) and strikingly high insulin release in response to glucose (7892 pmol/L) were found within weeks of the onset of the illness. The abnormality in insulin secretion occurred prior to the marked weight gain. Hyperinsulinemia was not accompanied by hypoglycemia. Early hyperinsulinemia may be a primary event in the development of hyperphagia and obesity following hypothalamic injury.

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The metabolic basis of weight gain in patients with hypothalamic obesity is incompletely understood because of the rarity of hypothalamic obesity and the lack of clinical investigative studies concerning the early stage of the illness. Hyperinsulinemia has previously been found in humans studied years after the onset of hypothalamic obesity. However, in most respects, patients with hypothalamic obesity show a similar pattern of carbohydrate tolerance and insulin secretion to that in patients with exogenous obesity.[1]

In experimental animals, ventromedial hypothalamic lesions induce a syndrome characterized by hyperphagia and obesity.[2] An analogous syndrome has been described in humans with pathologic processes that involve the basal medial hypothalamus.[3,4] Hyperphagia and obesity in the rats with ventromedial hypothalamic lesions are accompanied by an early rise in plasma insulin levels, prior to the onset of hyperphagia or obesity.[5] The hyperinsulinemia appears to be mediated by a direct action of vagal axons on beta cells in the pancreas.[6,7] Although it is unsettled whether hyperinsulinemia is the cause of the hyperphagia and obesity in the animal with a ventromedial hypothalamic lesion, the role of the central nervous system in the development of obesity is a topic of continued interest.[8]

Studies of the early events in hypothalamic obesity have not been done regarding humans. We recently had the opportunity to study a child who developed the rapid onset of hyperphagia and obesity following an episode of meningoencephalitis. Insulin levels early in the clinical course of the illness were strikingly abnormal. These observations were consistent with the hypothesis that the central nervous system has important influence on the secretion of pancreatic insulin in humans and that hyperinsulinemia may foster the development of

Table 1.—Initial Glucose Tolerance Test With Insulin Measurements 0.5 Month After Presentation (Weight, 37.5 kg)

Time, min	Glucose, mmol/L	Insulin (Normal Range), pmol/L
0	3.9	1183 (29-172)
30	8.3	7356 (179-1656)
60	8.5	8216 (129-1979)
120	4.0	3377 (115-1190)
180	3.0	954 (29-272)

Table 2.—Pharmacological Interventions 2.3 Months After Presentation (Weight, 47 kg)

	Glucose, mmol/L/Insulin,* pmol/L Levels		
Time, min	Before Medication	After Atropine (0.04 mg/kg/d, ×24 h)	After Diazoxide (10 mg/kg/d, ×24 h)
0	5.2/2122	5.3/1670	6.0/875
30	8.5/1348	12.7/1097	13.1/2144
60	11.4/3406	12.4/860	14.8/ . . .
120	15.0/5743	5.8/5377	8.6/4756
180	5.2/3821	3.0/1161	4.6/2201

*See Table 1 for normal insulin values.

Table 3.—Glucose Tolerance Tests With Insulin and Insulin C-Peptide Measurements

	10.7 mo (Weight, 70 kg)/11.6 mo (Weight, 63 kg) After Presentation		
Time, min	Glucose, mmol/L	Insulin, pmol/L	C-Peptide, μg/L
0	4.8/4.7	559/93	4.5/ . . .
30	9.1/6.0	5965/997	16.0/ . . .
60	6.6/4.6	2065/595	8.9/ . . .
120	3.3/5.8	459/394	3.7/ . . .
180	3.9/ . . .	. . .	. . .

the clinical syndrome of hypothalamic obesity.

REPORT OF A CASE

A 7-year-old boy presented with meningismus, papilledema, and mild left visual field neglect. His weight was 30 kg, and his height was 127 cm. The results of cerebrospinal fluid examination showed an opening pressure of 340 mm H_2O, a white blood cell count of 0.5×10^9/L (0.92 lymphocytes, 0.08 monocytes), a protein level of 1.28 g/L, and a glucose level of 2.5 mmol/L. An electroencephalogram showed bilateral, diffuse, background slowing, with attenuation of faster frequencies in the right posterior quadrant. Cranial computed tomography and magnetic resonance imaging were normal, with good visualization of the hypothalamus and third ventricular region. Herpes, mumps, leptospirosis, and *Mycoplasma* titers were unremarkable; cold agglutinins were negative. The Epstein-Barr virus titer was 1:1280, but the IgM titer was less than 1:10. The patient's first week of recovery appeared uneventful, except that the neurological consultant found him to be moderately uncooperative, with an exaggerated preoccupation with food.

He was discharged, but returned after 1 week, complaining of "eating and drinking constantly." He even ate vegetables, which he had previously disliked, but he did not eat nonfood items. He was described by his mother as becoming enraged when food was withheld, although not at inappropriate times. His weight had increased to 37.5 kg. He had abdominal distention with hepatomegaly and moderate tenderness over the liver. The results of neurological examination were normal, with resolution of the left neglect. It was noted that the patient would continue eating, even while cooperating with the examiner. A needle biopsy of the liver showed fatty infiltration. Baseline endocrine test results were as follows: T_4 thyroxine, 92 nmol/L (normal range, 58 to 155 nmol/L); T_3 resin uptake, 0.81 (normal range, 0.84 to 1.31); thyroid-stimulating hormone, 1.1 mIU/mL (normal range, 0.2 to 5.9 mIU/mL); morning plasma cortisol, 262 nmol/L (normal range, 166 to 690 nmol/L); and growth hormone, 276 pmol/L (normal level, <276 pmol/L). Prolactin level was mildly elevated (25 μg/L; normal range, 0 to 20 μg/L).

An oral glucose tolerance test revealed a normal glucose curve. However, baseline and stimulated insulin levels were markedly abnormal (Table 1). There were no symptoms suggestive of hypoglycemia during the test or at other times during the admission. Baseline growth hormone levels were undetectable, and there was no paradoxical rise of growth hormone in response to glucose.

The patient was discharged and readmitted 2.3 months after the onset of his illness for further evaluation. Basal metabolic rate was normal and caloric intake was approximately 6000 kcal/d. His weight had increased to 47 kg, and hyperphagia persisted. Oral glucose tolerance tests were repeated after 24-hour treatment with atropine and after 24 hours of diazoxide (Table 2). Carbohydrate tolerance had deteriorated, while insulin levels remained markedly elevated. The patient was discharged without pharmacological therapy.

Despite a trial of caloric restriction at home, the patient's weight climbed to 58 kg. Eighteen months after onset of the illness, the patient was readmitted for treatment with a strict diet of 700 kcal/d, which resulted in a weight loss of 7 kg. Hyperphagia persisted, although diminished, and the patient resumed weight gain at home to a peak of 74 kg, 10.4 months after the onset of the meningoencephalitis. A second inpatient trial of caloric restriction was attempted. Additional glucose tolerance tests were performed, which showed some "normalization" of insulin levels (Table 3). C-peptide levels were elevated, consistent with the level of insulin secretion. At the time of discharge, 3 months later, hyperphagia had considerably abated and his weight had dropped to 54 kg.

COMMENT

This young boy developed hyperphagia and obesity following an episode of meningoencephalitis. The clinical syndrome was consistent with hypothalamic obesity.[9] The postulated ventromedial hypothalamic damage may have occurred directly from the encephalitis[10] or indirectly from increased intracranial pressure.[9] Peripheral insulin levels were quite high, but the abrupt onset of the syndrome in association with the meningoencephalitis, the absence of hypoglycemia, and the gradual improvement of the hyperinsulinemia after a year do not support the presence of an insulin-secreting tumor. Inappropriate rage, which has been noted in experimental animals with ventromedial hypothalamic damage,[11] was not prominent in our patient, unless he was restricted from access to food. A similar pattern of behavior in a patient with a hamartoma invading the ventral hypothalamus has previously been reported.[3]

Hyperinsulinemia has been proposed as the major factor leading to hyperphagia and obesity in both humans and experimental animals with hypothalamic damage.[10,12] Bray and Gallagher[1] carefully examined humans with chronic obesity secondary to hypothalamic disease. In general, patients with hypothalamic obesity showed a glucose tolerance pattern and insulin response curve indistinguishable from those of individuals with exogenous obesity, ie, abnormal glucose tolerance, hyperinsulinemia, and insulin resistance. Obese patients with hypothalamic disorders, however, failed to normally suppress insulin in response to prolonged fasting.

The investigators concluded that hyperinsulinemia might be the initiating factor responsible for the hyperphagia and excessive fat deposition in these individuals.

Bucher et al[13] suggested that insulin might be responsible for the normal linear growth in patients who were deficient in growth hormone, following craniopharyngioma resection. They found an exaggerated insulin response to arginine infusions 1 year after tumor resection in children who exhibited excessive increase in height and weight. Early insulin measurements were not done, and glucose tolerance and insulin responses to glucose or fasting were not examined. Most of the patients in this subgroup were also noted to be hyperphagic, although this was not an invariable feature.

Our patient demonstrated interesting characteristics supporting the concept that hypothalamic regulation of insulin secretion is important in the evolution of hypothalamic obesity. Fasting hyperinsulinemia and exaggerated responses of insulin to glucose occurred early in the illness, preceding the development of massive weight gain.

Glucose tolerance was normal early in the course of his illness, and despite strikingly elevated insulin levels, there were no symptoms of hypoglycemia. Two months into his illness, the glucose tolerance tests showed a diabetic pattern, suggesting insulin resistance. Plasma cortisol level was normal, and the mechanism for the apparent insulin resistance was not clear. The early hyperinsulinemia could possibly have been the cause, rather than the consequence, of the obesity and hyperphagia.

Experimental[6] and clinical[14] studies have suggested that vagolytic therapy or vagotomy might be effective in modifying the weight gain in hypothalamic obesity. Pharmacological vagal blockade with the cholinergic antagonist, atropine, did not appreciably alter insulin responses in our patient. Diazoxide, which is used clinically to directly suppress insulin secretion by the pancreas,[15] also had no clear effect on the hyperinsulinemia. We did not have the opportunity to investigate the response of insulin to arginine infusion or fasting.

Unlike most cases of hypothalamic obesity, no other neurologic or neuroendocrine sequelae were noted in our patient.[10] Linear growth and sexual maturation will need to be closely monitored.

It is interesting that sequential examinations of this patient demonstrated a clinical and metabolic profile more closely resembling exogenous obesity. The biological determinants of most forms of obesity remain unknown, and the role of the central nervous system in caloric homeostasis is a topic of continuing interest.[8,12] Careful neuroendocrine examination of individuals with obesity associated with neurologic disorders may lead to better understanding of more common obesity problems.

References

1. Bray G, Gallagher TF. Manifestations of hypothalamic obesity in man: a comprehensive investigation of eight patients and a review of the literature. *Medicine.* 1975;54:301-330.
2. Heatherington AW, Ranson SW. Experimental hypothalamic-hypophyseal obesity in rat. *Proc Soc Exp Biol Med.* 1939;41:465-476.
3. Reeves AG, Plum F. Hyperphagia, rage, and dementia accompanying a ventromedial hypothalamic neoplasm. *Arch Neurol.* 1969;20:616-624.
4. Celesias G, Archer C, Chung HD. Hyperphagia and obesity: relationship to medial hypothalamic lesions. *JAMA.* 1981;246:151-153.
5. Frohman LA, Bernardis LL, Schnatz JD, Burek L. Plasma insulin and triglyceride levels after hypothalamic lesions in weanling rats. *Am J Physiol.* 1969;216:1496-1501.
6. Powley TL, Opsahl C. Ventromedial hypothalamic obesity abolished by subdiaphragmatic vagotomy. *Am J Physiol.* 1974;226:25-33.
7. Inoue S, Bray G, Mullen YS. Transplantation of pancreatic beta cells prevents development of hypothalamic obesity in rats. *Am J Physiol.* 1978;235:E266-E271.
8. Jennereaud B. An hypothesis on the aetiology of obesity: dysfunction of the central nervous system as a primary cause. *Diabetologia.* 1985; 28:502-513.
9. Bray G. Syndromes of hypothalamic obesity in man. *Pediatr Ann.* 1984;13:525-536.
10. Eaves EC, Croll MM. The pituitary and hypothalamic region in chronic epidemic encephalitis. *Brain.* 1930;53:56-75.
11. Wheatley MD. Hypothalamus and affective behavior in rats: study of effects of experimental lesions with anatomic correlations. *Arch Neurol.* 1944;52:296-316.
12. Bray G, Inoue S, Nishizawa Y. Hypothalamic obesity: the autonomic hypothesis and the lateral hypothalamus. *Diabetologia.* 1981;20:366-376.
13. Bucher H, Zapf J, Torresani J, et al. Insulin-like growth factors I and II, prolactin, and insulin in 19 growth hormone–deficient children with excessive normal, or decreased longitudinal growth after operation for craniopharyngioma. *N Engl J Med.* 1983;309:1142-1146.
14. Smith DK, Sarfeh J, Howard J. Truncal vagotomy in hypothalamic obesity. *Lancet.* 1983;2:1332-1333.
15. Fajans SS, Floyd JC. Diagnosis and medical management of insulinomas. *Ann Rev Med.* 1979; 30:313-329.

Right Parietal Stroke With Gerstmann's Syndrome

Appearance on Computed Tomography, Magnetic Resonance Imaging, and Single-Photon Emission Computed Tomography

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• We examined a patient who exhibited Gerstmann's syndrome (left-right disorientation, finger agnosia, dyscalculia, and dysgraphia) in association with a perioperative stroke in the right parietal lobe. This is the first description of the Gerstmann tetrad occurring in the setting of discrete right hemisphere pathologic findings. A well-localized vascular lesion was demonstrated by computed tomography, magnetic resonance imaging, and single-photon emission computed tomographic studies. The patient had clinical evidence of reversed functional cerebral dominance and radiologic evidence of reversed anatomic cerebral asymmetries.

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The localization of focal cerebral lesions causing the tetrad of symptoms—finger agnosia, left-right disorientation, agraphia, and acalculia—has been debated since Gerstmann's name was first attached to the syndrome.[1,2] In almost all cases with focal pathologic appearance, the lesion has been localized to the left parietal cortex (angular and second occipital gyri,[1-3] supramarginal gyrus, and superior parietal lobule[4]; superior angular, supramarginal, and inferior parietal gyri[5]; and posterior perisylvian region[6]). Strub and Geschwind,[7] reviewing all reported cases in the world literature through 1983, found only four instances in which discrete *right* hemisphere lesions were suspected. All of these cases, however, were reported prior to the computed tomographic (CT) era, and precise neuroanatomic localization based on their reported clinical features is difficult.

We present anatomic and metabolic studies demonstrating a right hemisphere lesion in a sinistral woman who exhibited Gerstmann's syndrome in association with a well-localized vascular lesion confirmed by CT, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT), indicating regional cerebral perfusion and metabolism. This case is unique to the literature in its extensive imaging of an underlying *right* parietal stroke.

REPORT OF A CASE

A 57-year-old left-handed white woman was seen 2 days after the operative placement of a single coronary artery bypass graft and primary closure of an atrial septal defect. During the first day postoperatively, her recovery seemed uneventful, although she did not speak very much. On the second postoperative morning, the staff noted that she seemed to be having some difficulty expressing herself, particularly with word finding, and a neurological consultation was requested.

Her medical history was notable for an inferior wall myocardial infarction 1 year prior to admission and mild hypertension. She had had no history of cerebrovascular accidents, transient ischemic attacks, or seizures and was neurologically intact on admission. The patient had a college education. The family history was notable for left-handedness in the patient's daughter.

The general medical examination was notable for a midline sternotomy incision. No carotid bruits or cardiac murmurs were observed.

On neurologic examination, the patient was alert, oriented, and cooperative. Attention was relatively intact (digit span, six forward and four backward, and preserved ability to name months backward). Language testing revealed occasional hesitancies in spontaneous speech, with mild word-finding difficulties and occasional literal and verbal paraphasic error. Prosody was preserved.

Repetition was also mildly impaired, with some hesitation and occasional paraphasic substitutions. Confrontation naming of objects in the room and elements of the examiner's clothing and body parts was performed with better than 90% accuracy. Comprehension was unimpaired, as demonstrated by appropriate verbal responses to questions and correct execution of simple and multiple-step directives.

Striking right-left confusion was noted. Any task that required right-left discrimination led to hesitation, frustration, and repeated errors in execution. She was unable to identify digits on either hand: she could not reliably name the digits and made frequent errors in trying to follow commands instructing her to identify or utilize a specific digit on her own hand or on the hand of the examiner. She was aware of her difficulty and was frustrated by it. This finger-naming difficulty was in sharp contrast with her only mildly impaired ability to name objects and colors on confrontation, including low-frequency items. She was unable to perform any calculations, exclaiming "I can't visualize the math." Even very simple calculations, such as adding 12 + 13 or determining the number of nickels in 75 cents, could not be carried out. She appeared to understand the task and began calculating mentally; she then became confused, lost track of her work, and needed to start over. Her performance did not improve with the use of pencil and paper.

Reading was significantly impaired. The patient read sentences out loud slowly, ef-

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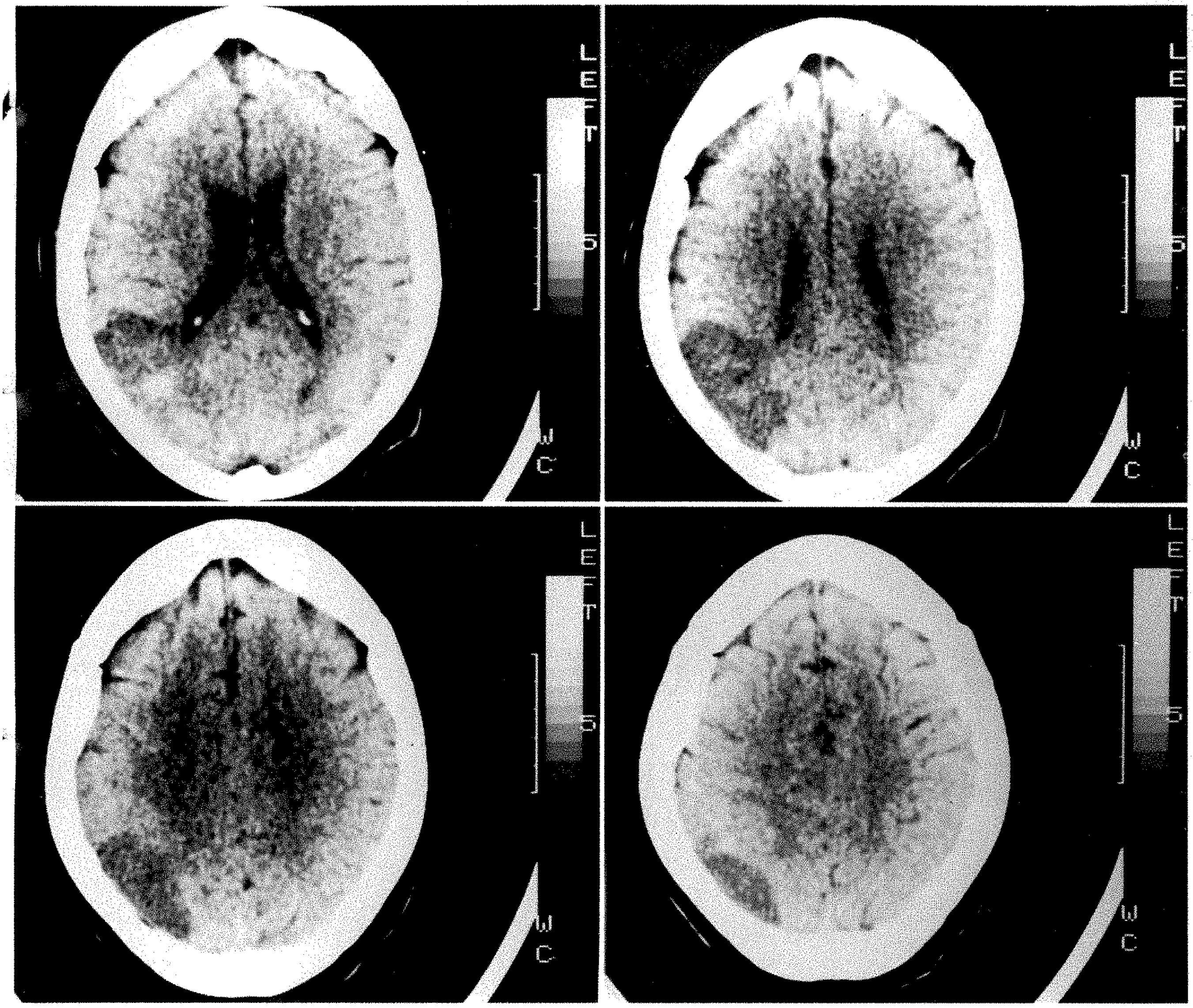


Fig 1.—Computed tomographic scans without intravenous contrast (axial, four adjacent 8-mm spaced images) taken on postoperative day 3 showing the right parieto-occipital low density in the angular gyrus (top left) extending superiorly just into inferior parietal gyrus and medially to the optic radiations.

fortfully, and monotonously, as if reading an unrelated list of words. Her comprehension of written passages was negligible. She was able to write only slowly and effortfully, with very poor penmanship, spelling errors, and omissions with drifting of the written line down and to the right on the page. When writing, she held her left hand in a "noninverted" posture. She evidenced no difficulty with constructions, drawing a clockface, and copying a cube with internal details accurately. Memory was unimpaired. She visually explored both sides of space, and there was no extinction to tactile simultaneous stimulation.

Results from the cranial nerve examination were notable for a left homonymous hemianopic visual field defect, denser in the inferior quadrant, and mild weakness of the lower face on the left side.

Examination of the extremities showed mild pronator drift of the left upper extremity but good strength on individual muscle-group testing and normal tone. Fine-motor control was unimpaired. Sensory testing to pin, touch, vibration, position, graphesthesia, and stereognosis was normal. Finger-to-nose, heel-to-shin testing was normal. Gait was normal. Reflexes were 1+ and symmetrical. Plantar responses were flexor.

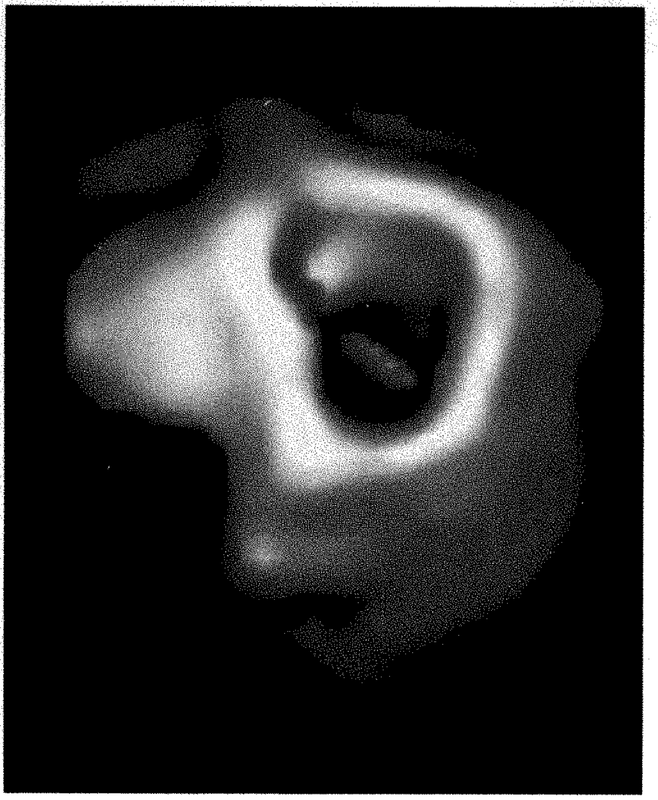
The patient scored −1.0 on the modified Oldfield handedness battery.

A perioperative cerebrovascular accident in the right middle cerebral distribution was suspected. A CT scan without contrast (Fig 1) on postoperative day 3 revealed a discrete right parieto-occipital wedge-shaped hypodensity (5 × 2.5 cm) in the angular gyrus. The area of lucency began at the level of the ventricular atrium and extended superiorly through three adjacent 8-mm axial CT images to the inferior parietal lobule and medially to the optic radiations.

On postoperative day 4, the patient's speech was fluent without paraphasic errors, and she had only minimal difficulty in repeating long gramatically complex sentences. Her facial asymmetry had resolved, and the field defect had improved to a moderate left inferior quadrant anopsia.

The patient underwent SPECT neuroimaging studies on postoperative day 7 with hexamethyl propylenamine oxime (technetium Tc 99m–HMPAO). The isotope uptake at 20 minutes after the injection shows a defect on axial view (Fig 2) of equivalent size to the hypodensity on CT scan. The three-dimensional surface reconstruction (Fig 3) places the hypoperfused region in the superior right parieto-occipital cortex (posterior angular gyrus) and underlying white matter.

On postoperative day 9, the patient underwent a cranial MRI scan in multiple planes for further evaluation of the vascular lesion. Figure 4 shows the coronal and axial images. The cerebral gyri are identified and show an



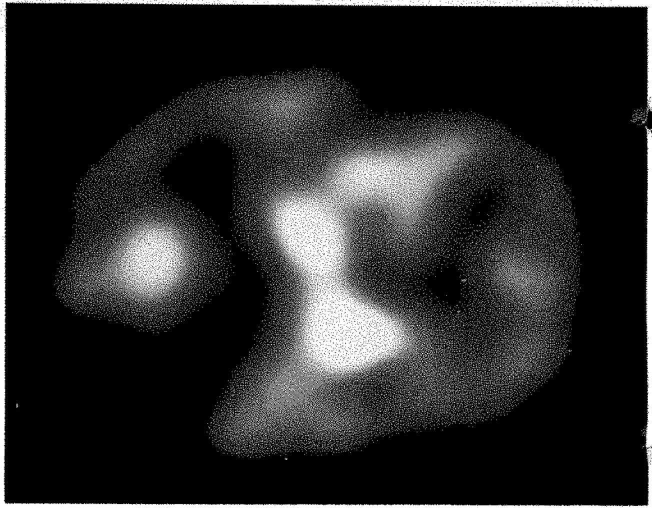


Fig 2.—Single-photon emission computed tomographic/hexamethylpropyleneamine (HM-PAO) axial image 20 minutes after injection on postoperative day 7. Note the similar perfusion defect in the right parieto-occipital region (patient's right on left of image). Color scale is such that yellow indicates regions with greatest HM-PAO concentration and dark blue indicates lowest HM-PAO activity.

Fig 3.—Three-dimensional surface reconstruction of the single-photon emission computed tomographic/hexamethylpropyleneamine images shown in Fig 2, viewed from the right posterior oblique angle. Note the shape and extensive defect inferior and posterior to the angular gyrus.

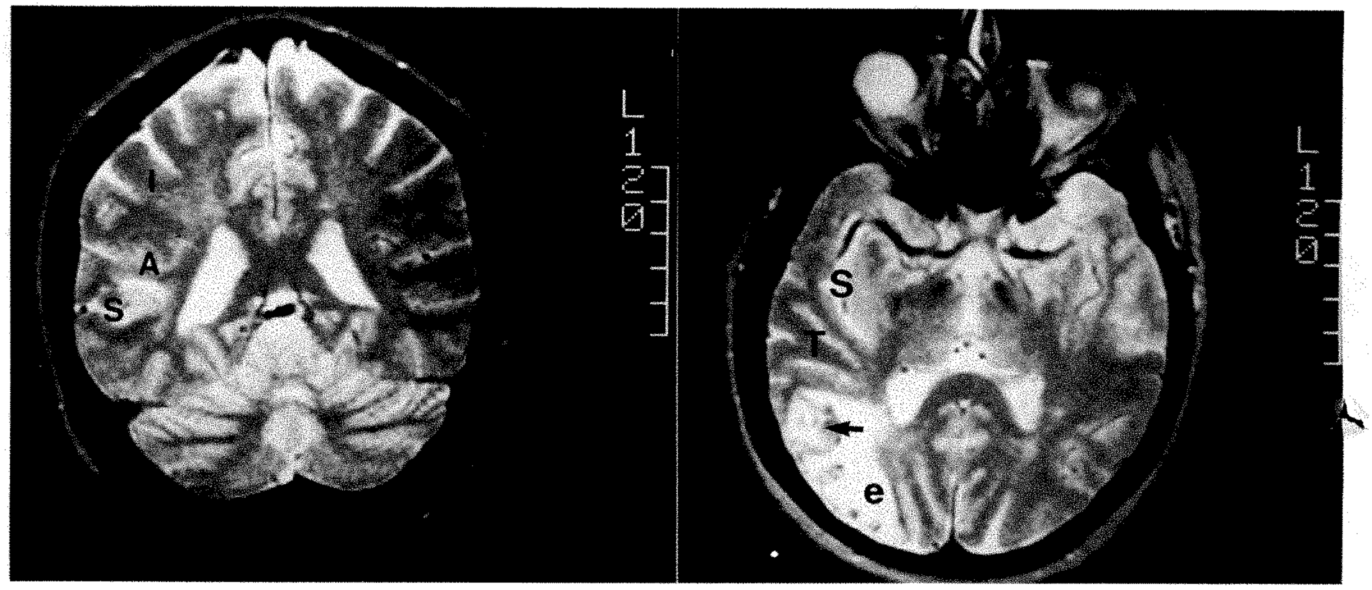


Fig 4.—Left, Magnetic resonance imaging (MRI), modified coronal plane (TR, 2000 milliseconds; TE, 35 milliseconds), anterior extent of increased signal of lesion. Inferior parietal gyrus (I), angular gyrus (A), and sylvian fissure (S) are indicated. Right, MRI, modified axial plane (TR, 2000 milliseconds; TE, 70 milliseconds), imaging through temporo-occipital lobes shows an area of heterogeneous cortical signal (arrow) in posterior inferior angular gyrus with extension of increased signal intensity (edema[e]) to adjacent occipital gyrus. The temporal operculum (T) and sylvian fissure (S) are shown.

area of heterogeneous cortical signal in the posterior inferior angular gyrus with extension of increased signal intensity (edema) to adjacent occipital gyri.

Both MRI and CT images were analyzed for anatomic asymmetries that have been proposed to correlate with functional cerebral asymmetry.[8,9] Standardized methods were employed to analyze sylvian fissure course,[10] fronto-occipital petalias,[11-13] and size of planum temporale (modified).[14] Each of these techniques demonstrated a reversal of the most common pattern of asymmetry found in right-handed subjects: (1) the posterior sylvian fissure on the right extended more horizontally and posteriorly than it did on the left (demonstrated in Fig 4, left); (2) on both MRI and CT studies, left frontal and right occipital lobes exhibited greater width and length (petalia) than did their counterparts; and (3) asymmetry of the posterior opercular demarcation, consistent with a larger planum temporale in the right hemisphere than in the left, was noted.

COMMENT

It is recognized that the four components of Gerstmann's syndrome in an individual patient may manifest to a variable degree.[7] In our patient, finger agnosia and left-right disorientation were prominently affected. Her agraphia, characterized by paragraphia with mispellings and syntax errors and spatial dysgraphia (poor word alignment across a page), was mild. Her acalculia was also severe, and of the type, anarithmetria,[2,7,15] that is most commonly associated with Gerstmann's syndrome. Additionally, our patient exhibited alexia and a mild posterior aphasia—deficits that have been noted to not infrequently accompany Gerstmann's tetrad (the *angular gyrus syndrome*). The major impairment in finger identification, left-right discrimination, and calculations was disproportionate to the mild deficit in oral language function. Evidence of constructional apraxia or hemispatial neglect was absent.

We believe that ours is the first patient to be described with Gerstmann's syndrome resulting from a focal right hemisphere lesion that has been fully documented by CT, MRI, and SPECT studies. Strub and Geschwind's[7] review of all reported cases through 1983 noted only four patients suggested to have discrete right hemisphere lesions, with 68 patients with left hemisphere lesions, 20 with bilateral lesions, and four with either left hemisphere or bilateral lesions. Our review of the literature since has yielded no additional right hemisphere cases. All four right hemisphere cases preceded the advent of modern neuroimaging. The two patients described by Heimberger et al[16] are listed in a table but are not clearly identified in the accompanying individual case descriptions. It appears likely that one of the cases they listed as right hemisphere was a patient described as having a large right hemisphere glioblastoma with midline shift and an electroencephalogram displaying slowing on the left side; thus, this patient almost certainly had undergone a pathologic event bilaterally. Heimberger et al[16] provided no detailed description of a second patient with clinical evidence of a discrete right hemisphere lesion. In Kinsbourne and Warrington's[17] case, localization was based on accompanying clinical signs and electroencephalographic findings—no confirmatory anatomic studies were provided. Hermann and Potzl's[18] 1926 case had a right occipital tumor discovered at surgery, without exploration or postmortem examination of the left hemisphere to exclude a bilateral process.

Gerstmann suggested that the symptom cluster of finger agnosia, right-left disorientation, agraphia, and acalculia indicated lesions in the dominant parietal lobe, situated in the great proportion of right-handers and most left-handers in the left hemisphere. We hypothesize that our patient had strongly reversed functional cerebral lateralization so that a right parietal lesion could produce the constellation of signs of Gerstmann's syndrome. Our patient was strongly left-handed (modified Oldfield handedness score, −1). A family history of left-handedness in a first-degree relative was known. (Evidence of a genetic component to determination of handedness has been reviewed by Levy.[19]) The patient wrote with a noninverted hand posture, which has been suggested to indicate likely contralateral hemispheric (here, right hemispheric) dominance for speech.[20] The patient also experienced alexia and mild posterior aphasia following her isolated right hemisphere insult, further suggesting that she had had major representation of language function in the right hemisphere.

Moreover, a number of investigators have identified anatomic asymmetries that may correlate with functional cerebral asymmetry.[8-14] Our patient exhibited reversed asymmetry for several of these anatomic findings. The posterior sylvian fissure on the right extended more horizontally and posteriorly than did its counterpart, suggesting that the temporal and parietal opercula were larger on the right than on the left. The planum temporale, a major component of the temporal speech region of Wernicke, was larger in the right hemisphere than in the left. Thus, our patient exhibited both a pattern of anomalous functional motoric and linguistic dominance and a reversal of anatomic brain asymmetries that may comprise the biologic substrate of functional lateralization.

In addition to the variable deficit severity of each component in Gerstmann's syndrome,[7] some have remarked that deficit improvement occurs at different rates longitudinally.[21] Similarly, we noted improvement in this patient's writing ability and right-left orientation at 1 week postoperatively (postvascular event).

In this well-documented instance of a focal right hemisphere lesion producing Gerstmann's syndrome, the pathologic event was situated primarily in the posterior parietal lobe. Thus, this case provides further evidence to supplement the findings drawn from numerous previously reported left hemisphere cases that the lesion most likely to produce Gerstmann's syndrome is placed in the dominant posterior parietal region.

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References

1. Gerstmann J. Fingeragnosie und isolierte Agraphie, ein neues Syndrom. *Z Gesamte Neurol Psychiatrie*. 1927;108:381-402.
2. Gerstmann J. Syndrome of finger agnosia, disorientation for right and left, agraphia and acalculia. *Arch Neurol Psychiatry*. 1940;44:398-408.
3. Levine DN, Mani RB, Calvanio R. Pure agraphia and Gerstmann's syndrome as a visualspatial-language dissociation: an experimental case study. *Brain Lang*. 1988;35:172-196.
4. Hrebek V. Pathophysiologic interpretation of Gerstmann's syndrome: definition of new broader syndrome of interparietal disconnection: their value for topical diagnostics of lesions in the dominant cerebral hemisphere: *Neuropsychologia*. 1977;11:377-388.
5. Roeltgen DP, Sevush S, Heilman KM. Pure Gerstmann's syndrome from a focal lesion. *Arch Neurol*. 1983;40:46-47.
6. Morris HH, Luder H, Lesser RP, Dinner DS, Hahn J. Transient neuropsychological abnormalities (including Gerstmann's syndrome) during cortical stimulation. *Neurology*. 1984;34:877-883.
7. Strub RL, Geschwind N. Localization in Gerstmann syndrome. In: Kertesz A, ed. *Localization in Neuropsychology*. New York, NY: Academic Press Inc; 1983:295-321.
8. Geschwind N, Levitsky W. Human brain: left-right asymmetries in temporal speech region. *Science*. 1968;161:186-187.
9. Geschwind N, Galaburda AM. Cerebral lateralization. *Arch Neurol*. 1985; 42:428-459.
10. Damasio H, Damasio AR. *Lesion Analysis in Neuropsychology*. New York, NY: Oxford University Press Inc; 1989:133.
11. Pienadz JM, Naeser MA. Computed tomographic scan cerebral asymmetries and morphologic brain asymmetries. *Arch Neurol*. 1984;41:403-409.
12. Bear D, Schiff D, Saver J, Greenberg M, Freeman R. Quantitative analysis of cerebral asymmetries: fronto-occipital correlation, sexual dimorphism, and association with handedness. *Arch Neurol*. 1986;43:598-603.
13. Kertesz A, Black SE, Polk M, Howell J. Cerebral asymmetries on magnetic resonance imaging. *Cortex*. 1986;22:117-127.
14. Stratta P, Rossi A, Gallucci M, Amicarelli I, Passariello R, Casacchia M. Hemispheric asymmetries and schizophrenia: a preliminary magnetic resonance imaging study. *Biol Psychiatry*. 1989;25:275-284.
15. Hecaen H, Angelergues R, Houllier S. Les varietes cliniques des acalculies au cours des lesions retro-roladiques: approche statistique du probleme. *Rev Neurol*. 1961;105:85-103.
16. Heimburger RF, Demyer W, Reitan RM. Implications of Gerstmann's syndrome. *J Neurol Neurosurg Psychiatry*. 1964;27:52-57.
17. Kinsbourne M, Warrington EK. A study of finger agnosia. *Brain*. 1962;85:47-66.
18. Hermann G, Potzl O. Über die Agraphie und ihre lokaldiagostischen Beziehungen. Berlin, Germany: S Karger AG; 1926.
19. Levy J. A review of evidence for a genetic component in the determination of handedness. *Behav Genet*. 1976;6:429-453.
20. Levy J, Reid M. Variations in writing posture and cerebral organization. *Science*. 1976;194:337-339.
21. Varney NR. Gerstmann syndrome without aphasia: a longitudinal study. *Brain Cogn*. 1984;3:1-9.

Neurologic Complications of the Tryptophan-Associated Eosinophilia-Myalgia Syndrome

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• A case of tryptophan-associated eosinophilia, central nervous system complications, and multiple white matter lesions by magnetic resonance imaging is presented. Eosinophilia regardless of its cause should be included within the differential of patients exhibiting periventricular white matter lesions.

(*Arch Neurol.* 1991;48:436-438)

In November 1989, an article disclosed an epidemic of eosinophilia-myalgia syndrome first recognized in New Mexico,[1] but subsequently noted to be widely distributed across the entire United States.[2] The condition was associated with the ingestion of the essential amino acid tryptophan. The pathogenic mechanisms underlying this association have yet to be elucidated.

Symptoms reported included myalgia, subjective weakness, fever, arthralgia, dyspnea, rash, edema, and pneumonia. This was by definition accompanied by an eosinophilic leukocyte count of more than 2×10^9/L.[1] Thirteen deaths have been attributed to this condition.[3]

REPORT OF A CASE

A 46-year-old white woman was admitted to a community hospital on October 19, 1989, for right-sided weakness. One week prior she had fallen, landing on her coccyx. A few days later she developed right arm and face numbness and weakness with progression to the right leg by the day of admission.

The only medication that she claimed to be taking on admission was vitamin E. Her medical history was unremarkable. She had a 25-pack-year history of smoking, but no history of alcohol or drug abuse. On review of systems, she reported recent onset of frontal headache, blurred vision, and right shoulder aches.

On initial examination she was not in acute distress and had normal vital signs. Examination of her skin disclosed a streaky, erythematous rash over the buttocks and legs. On neurologic examination, her mental status was normal. Cranial nerve testing revealed a mild right central seventh nerve palsy and diminished sensitivity to sharp stimuli over the right side of her face. The patient's strength was graded 0/5 in the right upper extremity and 4/5 in the right lower extremity. Reflexes were 2+ throughout and plantar responses were flexor. Sensory examination demonstrated decreased perception of sharp stimuli on the right side of her body. There were no abnormal cerebellar signs. She had a right hemiparetic gait. The remainder of the physical examination was unremarkable.

Results of admission laboratory investigations were significant for a white blood cell count of 19.4×10^9/L (normal, 4 to 10×10^9/L), with a differential of 0.5 segmented neutrophils (normal, 0.54 to 0.62), 0.15 lymphocytes (normal, 0.25 to 0.33), 0.03 monocytes (normal, 0.01 to 0.13), and 0.32 eosinophils (normal, 0.01 to 0.05). Results of the liver function tests were nonspecifically abnormal.

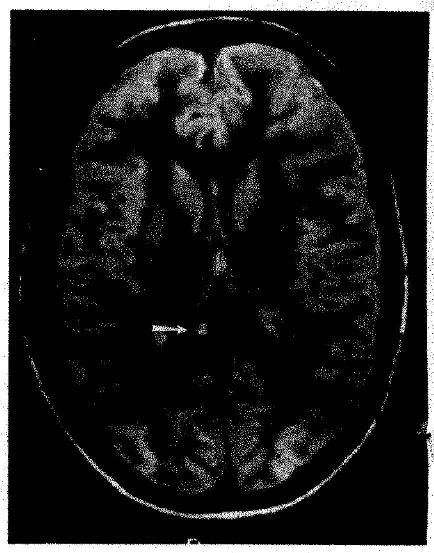
An initial computed tomographic scan of the head with and without contrast demonstrated an irregular area of decreased attenuation in the deep left frontal lobe without enhancement or mass effect, suggesting an ischemic infarct. Her two-dimensional echocardiogram and carotid duplex ultrasound studies were unremarkable.

A lumbar puncture was performed with the following results: protein, 0.69 g/L (normal, 0.15 to 0.45 g/L); glucose, 3.4 mmol/L (normal, 2.2 to 4.4 mmol/L); white blood cells, 0.001×10^9/L (normal, 0 to 0.005×10^9/L); and red blood cells, 7×10^{12}/L (normal, 0 to 10×10^{12}/L). *Trichinella* serologic examination and stool for ova and parasites were negative. An evaluation for occult malignancy included a chest roentgenogram, abdominal computed tomographic scan, and mammogram, all of which were negative. A vasculitis screen included the following: erythrocyte sedimentation rate, serum protein electrophoresis, antinuclear antibody, and rheumatoid factor, all of which were normal. Serum human immunodeficiency virus, toxoplasmosis, coccidioidomycosis, and *Aspergillus* titers as well as VDRL and *Candida* antigen assays were negative.

A magnetic resonance imaging scan of the head disclosed multiple focal areas of abnormally increased signal intensity within the deep white matter and corpus callosum (Figs 1 through 3) as well as a focal area of increased signal intensity within the left parietal lobe.

The patient was transferred to the University Medical Center in Tucson, Ariz, on October 26, 1989, for further investigation. The examination at the time of transfer revealed a spastic right hemiparesis and bilateral Babinski signs. Based on the magnetic resonance imaging appearance, which raised the possibility of multiple sclerosis, a second lumbar puncture was performed and showed the following results: protein, 0.3 g/L; glucose, 3.9 mmol/L; white blood cell count, 0.008×10^9/L (0.99 monocytes); red blood cell count, 3×10^{12}/L; IgG, 0.018 g/L (normal, 0.01 to 0.04 g/L); and two distinct oligoclonal bands. Visual evoked responses were normal, and median somatosensory responses revealed only slowing of intracortical conduction consistent with the patient's left-sided symptomatic lesion. An electroencephalogram was normal. Dis-

Fig 1.—This T$_2$-weighted axial magnetic resonance image shows an abnormal area of increased signal (arrow) in the right side of the splenium of the corpus callosum (TR = 2500, TE = 30, 0.6 Tesla).



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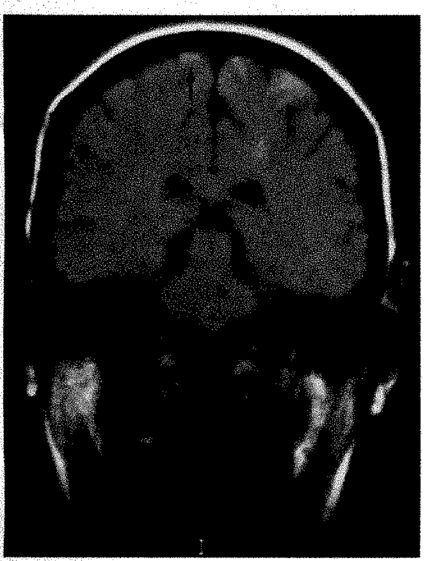

Fig 2.—Abnormal areas of cortical signal (arrows) are present in the parietal lobes (TR = 600, TE = 20, 0.6 Tesla).

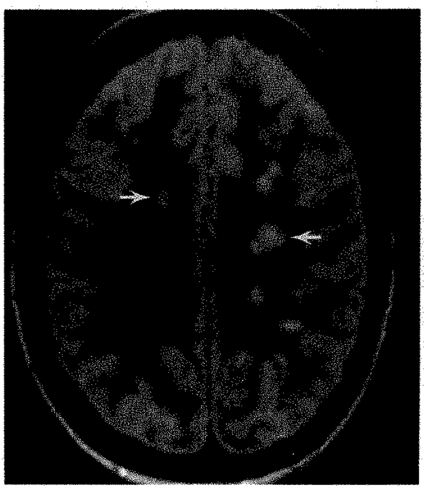

Fig 3.—Bilateral areas of abnormally increased signal (arrows) are demonstrated in the centrum semiovale (TR = 2500, TE = 30, 0.6 Tesla).

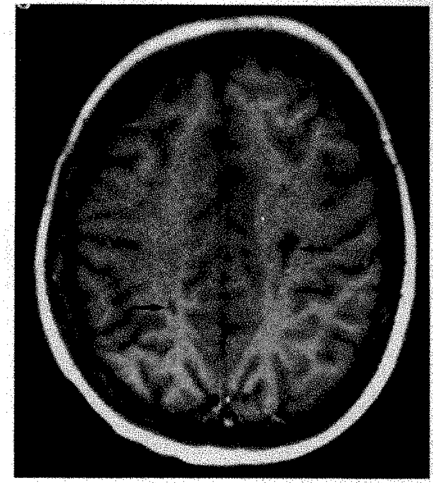

Fig 4.—Follow-up scan showing punctate encephalomalacia (arrow) where acute lesions had been (TR = 600, TE = 20, 0.6 Tesla).

charge diagnoses were possible multiple sclerosis vs eosinophil-induced neurotoxicity, and peripheral eosinophilia of unclear etiology.

Approximately 1 month later, when news reports of tryptophan associated with eosinophilia surfaced in the lay press, the patient disclosed that she had been taking 1.5 to 2 g of tryptophan at bedtime for the preceding 4 to 6 months. Use of the drug had been inadvertently discontinued on admission to the hospital. No treatment was given, and she has had no further neurologic events. Five months after initial presentation her white blood cell count was 10.8×10^9/L, with 0.1 eosinophils, signifying a reduction in her absolute eosinophil count from 6208 to 1080 cells. However, at this point the patient returned with an erythematous, edematous lower extremity rash and sclerotic plaques consistent with eosinophilic fasciitis (confirmed by skin and muscle biopsy). The creatine kinase level was normal; however, the aldolase level was elevated to 45 U/L (normal, 0 to 6 U/L). She was agreeable to starting steroids. A follow-up magnetic resonance imaging 5 months after presentation revealed that the previously noted white matter lesions had diminished in size and evolved into small infarcts (Fig 4).

COMMENT

Our patient has been extensively evaluated excluding the usual causes of eosinophilia other than the ingestion of tryptophan. The distribution of the patient's multiple central nervous system lesions is highly atypical of multiple sclerosis due to their location within the splenium of the corpus callosum and within the cerebral gray matter. Likewise, the evolution of the lesions on magnetic resonance imaging is atypical for multiple sclerosis and is more suggestive of small infarctions. The clinical course was one of a subacute monophasic progressive illness, which would speak against a diagnosis of clinically definite multiple sclerosis. The two oligoclonal bands may represent a nonspecific inflammatory reaction. Therefore we believe this to be the first reported case of central nervous system involvement by tryptophan-associated hypereosinophilia.

As of February 9, 1990, there had been 1269 cases of tryptophan-associated eosinophilia reported in the United States.[3] Due to the frequent complaint of muscle pain, the disease has been called the eosinophilia-myalgia syndrome. The current median age of those affected is 48 years, and the median dose of tryptophan is 1500 mg/d. Eighty-four percent are female and 96% are non-Hispanic whites.[4] Rash and edema have been reported in over 50%.[1,3] Elevated liver function tests were noted in 51%.[3] Our patient fits the demographic pattern; however, she has a pronounced central nervous system involvement and an absence of severe myalgias.

A review of the literature revealed reports of peripheral and central nervous system involvement by the idiopathic hypereosinophilia syndrome. With respect to the peripheral nervous system, clinical patterns of multiple mononeuropathy, distal symmetrical motor neuropathy, distal symmetrical sensory neuropathy, and radiculopathy have been reported.[5-9] Nerve biopsy or autopsy has shown a variety of histopathologic findings consistent with wallerian degeneration,[9] axonal degeneration,[5] demyelination, and vasculitis.[6] The pathogenetic mechanisms proposed have included ischemia on either a vasculitic[5-7] or cardioembolic basis,[7] and also neurotoxicity.[5,7,9]

With regard to the central nervous system, clinical patterns of seizures,[7] dementia,[7,9,10] and cerebral infarction[7,9] have been described. Computed tomographic scans in these cases have shown infarcts,[9] areas of contrast enhancement,[7] atrophy,[7,9] and the appearance of demyelination.[7] In 1989 Kaplan reported a case with periventricular areas of increased signal intensity on magnetic resonance imaging. The pathogenetic mechanisms postulated include thromboembolization,[7-9] eosinophil infiltration,[9] and neurotoxicity.[7,9,10]

Although the term *neurotoxicity* initially seems rather indefinite, it has been well established that the eosinophil contains cytotoxic granules that release eosinophil cationic protein (partially responsible for thromboembolism), neurotoxic protein, and major basic protein.[11] In 1979 Durack et al[12] injected cells from patients with hypereosinophilic syndromes into either the cerebral hemisphere or subarachnoid space of rabbits and guinea pigs. Examination of the brains revealed loss of Purkinje cells, spongy degeneration of the cerebellum, brain stem and spinal cord, and an occasional axonal degeneration of the peripheral nerves. It seems reasonable to hypothesize that these toxic granules played a pathogenic role in our patient, perhaps by creating a vasculitis leading to microinfarctions.

Although tryptophan itself has been

demonstrated to exhibit in vitro a direct neurotoxicity, probably related to indoleamine dioxygenase metabolites,[13-15] we believe that the weight of evidence favors a role played by the eosinophilia documented in this patient.

It should be noted that although tryptophan was discontinued at the time of the initial admission, the peripheral eosinophilia only gradually improved, leaving an eosinophilic fasciitis 5 months after presentation. This observation would lend support to early aggressive steroid therapy.

We presented a patient, whose clinical presentation was suggestive of a stroke syndrome, but in whom there existed striking eosinophilia and multiple central nervous system lesions demonstrated by magnetic resonance imaging. To our knowledge this represents the first reported case of central nervous system involvement due to tryptophan-associated eosinophilia. This case illustrates the importance of specifically inquiring about the ingestion of tryptophan during the evaluation of a patient with multiple white matter lesions, as patients may not volunteer information about their use of nonprescription medications.

References

1. Centers for Disease Control. Eosinophilia-myalgia syndrome: New Mexico. *MMWR.* 1989;38:765-767.
2. Centers for Disease Control. Update. Eosinophilia-myalgia syndrome associated with ingestion of L-tryptophan: United States. *MMWR.* 1989;38:842-843.
3. Centers for Disease Control. Clinical spectrum of eosinophilia-myalgia syndrome: California. *MMWR.* 1990;39:89-91.
4. Centers for Disease Control. Update. Eosinophilia-myalgia syndrome associated with ingestion of L-tryptophan: United States. *MMWR.* 1990;39:14-15.
5. Dorfman LJ, Ransom BR, Forno LS, Kelts A. Neuropathy in the hypereosinophilic syndrome. *Muscle Nerve.* 1983;6:291-298.
6. Grisold W, Jellinger K. Multifocal neuropathy with vasculitis in hypereosinophilic syndrome: an entity or drug-induced effect? *J Neurol.* 1985;231:301-306.
7. Moore PM, Harley JB, Fauci AS. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. *Ann Intern Med.* 1985;102:109-114.
8. Martin-Gonzalez E, Yebra M, Garcia-Merino A, Liano H. Neurologic dysfunction in the idiopathic hypereosinophilic syndrome. *Ann Intern Med.* 1986;104:448-449.
9. Weaver DF, Heffernan LP, Purdy RA, Ing VW. Eosinophil-induced neurotoxicity: axonal neuropathy, cerebral infarction, and dementia. *Neurology.* 1988;38:144-146.
10. Kaplan PW, Waterbury L, Kawas C, Bolla-Wilson K, Durack D. Reversible dementia with idiopathic hypereosinophilic syndrome. *Neurology.* 1989;39:1388-1391.
11. Fauci AS, Harley JB, Roberts WC, Ferrans VJ, Gralnick HR, Bjornson BJ. The idiopathic hypereosinophilic syndrome: clinical, pathophysiologic, and therapeutic considerations. *Ann Intern Med.* 1982;97:78-92.
12. Durack DT, Sumi SM, Klebanoff SJ. Neurotoxicity of human eosinophils. *Proc Natl Acad Sci USA.* 1979;76:1443-1447.
13. Freese A, Schwartz KJ, During M. Potential neurotoxicity of tryptophan. *Ann Intern Med.* 1988;108:312-313.
14. Silver RM, Heyes MP, Maize JC, Quearry B, Vionnet-Fausset M, Sternberg EM. Scleroderma, fasciitis, and eosinophilia associated with the ingestion of tryptophan. *N Engl J Med.* 1990;322:874-881.
15. During MJ, Freese A. Is L-tryptophan safe? *Aust N Z J* Psychiatry. 1988;22:339.

Magnetic Resonance Imaging of Fourth Ventricular Epidermoid Tumors

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• Two pathologically proved cases of epidermoid tumor of the fourth ventricle are presented; clinical history and computed tomographic, magnetic resonance imaging, and histopathologic findings are included.

(*Arch Neurol.* 1991;48:438-440)

Epidermoid tumors arise from the inclusion of ectodermal elements at the time of closure of the neural groove, resulting in a heterotopia of such elements. Within the central nervous system, these tumors occur most frequently in descending order in the cerebellopontine angle, parapituitary region, diploe, fourth ventricle, petrous bone, and intraspinal space.[1] The name *pearly tumor* has been applied to this tumor because its smooth capsular surface sometimes has a mother-of-pearl appearance. It has also been called a cholesteatoma because the soft, white, waxy material that makes up the tumor is rich in cholesterol crystals. This material is the result of progressive desquamation and breakdown of keratin from the epithelial lining of the cyst. Numerous reports describing the computed tomographic (CT) findings of fourth ventricular epidermoid tumors generally agree that these tumors cause dilatation of the fourth ventricle, have a density less than water but greater than fat, and show no evidence of contrast enhancement.[2-6] Both cases in this report showed similar CT characteristics, and on magnetic resonance imaging (0.5 T), the tumors were hypointense relative to brain parenchyma on T_1-weighted images (short repetition time; short echo time) and hyperintense on T_2-weighted images (long repetition time; long echo time).

REPORT OF CASES

CASE 1.— A 60-year-old man had a 15-year history of dizziness, but in the few months prior to surgery he became ataxic enough to warrant the use of a cane, and he complained of mild headaches. On examination, it was observed that he had sustained nystagmus on right and left lateral gaze, with moderate upbeat nystagmus. His gait was broad based, and appendicular testing of the upper extremities revealed mild decreased function. The findings of the remainder of the examination were normal. A CT scan showed a low-density, nonenhancing, well-marginated mass within an expanded fourth ventricle, associated with hydrocephalus (Fig 1, top left). Magnetic resonance imaging showed a well-marginated, homogeneously low-signal mass within the fourth ventricle on sagittal (Fig 1, top right) T_1-weighted images. On axial T_2-weighted images, the mass was hyperintense and there was no peritumoral edema (Fig 1, bottom left). At surgery, a white tumor with the consistency of cottage cheese

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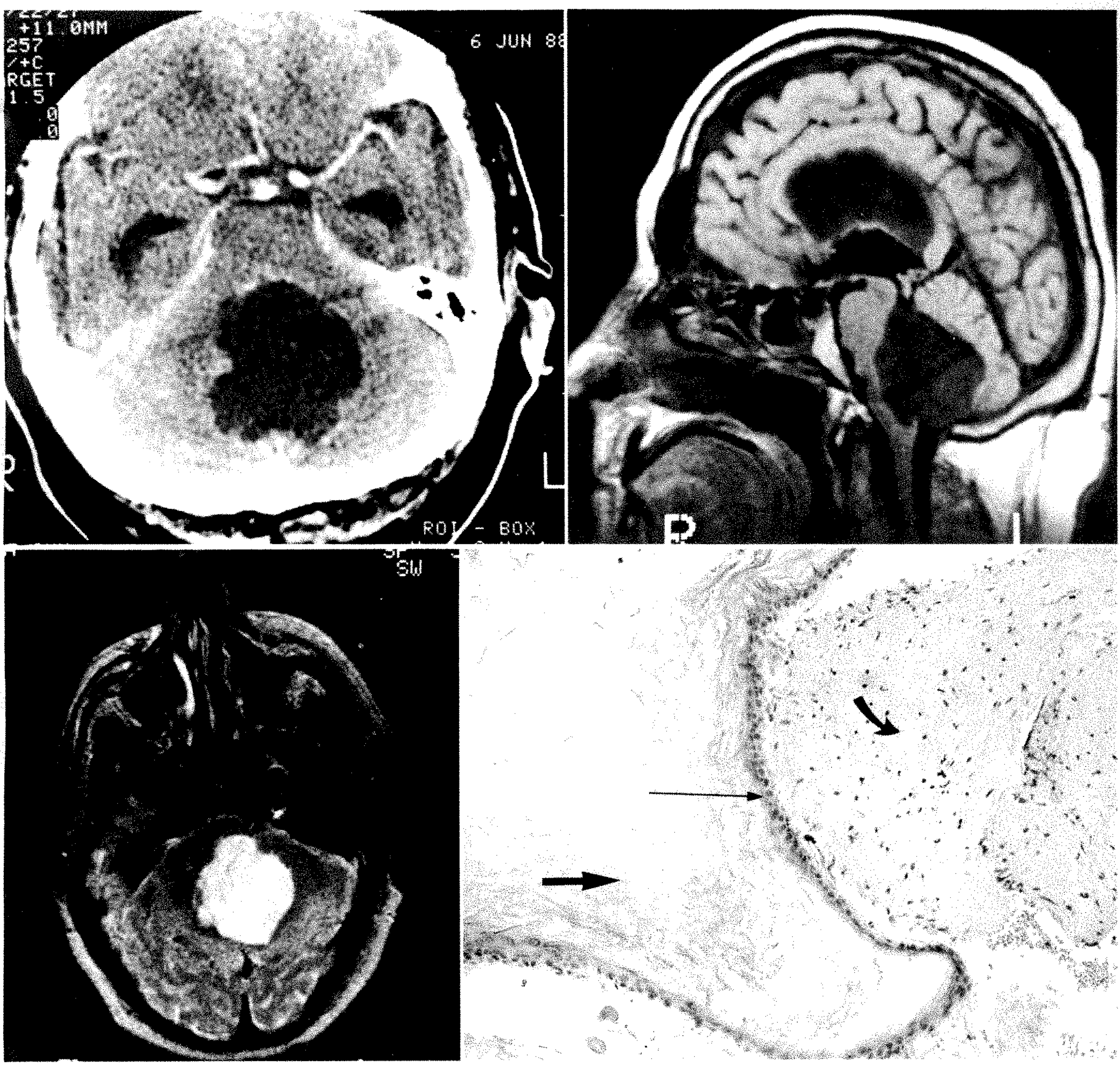

Fig 1.—Top left, Enhanced computed tomographic scan shows well-marginated, nonenhancing, low-density mass within the fourth ventricle. Top right, Sagittal magnetic resonance image (short repetition time; short echo time) shows low-signal tumor within the fourth ventricle with compression of the brain stem and cerebellum. Bottom left, Axial magnetic resonance image (long repetition time; long echo time) shows high-signal tumor within the fourth ventricle. Bottom right, Black-and-white photomicrograph (high magnification) of a hematoxylin-eosin preparation showing lamellar keratin debris (heavy straight arrow), stratified squamous epithelium (long thin arrow), and outer layer of collagenous material (curved arrow).

was present within the fourth ventricle, clearly separated from the cerebellar hemispheres and vermis. The microscopic appearance of the tumor was typical of an epidermoid. The lining of the cyst was composed of a simple stratified squamous epithelium supported by an outer layer of collagenous tissue. Progressive exfoliation of keratinous material toward the interior of the cyst produced the characteristic lamellar appearance (Fig 1, bottom right).

Case 2.— A 44-year-old woman presented with several months of ataxia. On physical examination, she had diplopia, nystagmus on extreme lateral gaze to either side, and mild appendicular ataxia in the right arm and leg. The findings of the remainder of the neurologic examination were normal. Magnetic resonance imaging demonstrated findings identical to those in case 1. On the sagittal T_1-weighted image (Fig 2, top), the fourth ventricular tumor had low-signal intensity, and on the axial T_2-weighted image, it demonstrated homogeneously high-signal intensity without peritumoral edema (Fig 2, bottom). An angiogram (not shown) showed mass effect without evidence of stain, and a CT scan (not shown) showed a nonenhancing, low-density mass within the fourth ventricle. At surgery, an exophytic white tumor was found in the fourth ventricle, and the findings of gross inspection were consistent with an epidermoid tumor. Histologic examination demonstrated the characteristic findings of an epidermoid tumor, similar to those seen in Fig 1, bottom right.

COMMENT

The CT characteristics of epidermoid tumors of the fourth ventricle

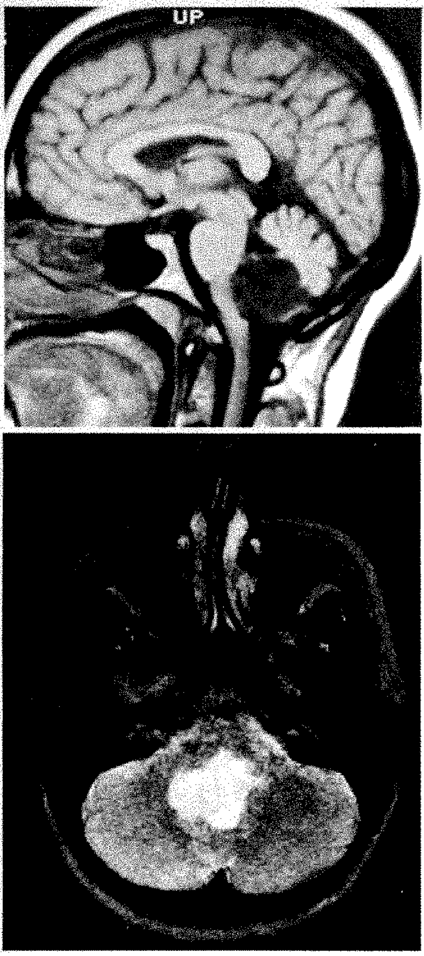

Fig 2.—Top, Sagittal magnetic resonance image (short repetition time; short echo time) shows expansion of the fourth ventricle by a low-signal mass. Bottom, Axial magnetic resonance image (long repetition time; long echo time) shows high-signal tumor.

have been described in detail.[2-6] Smooth margination, mass effect, and lack of peritumoral edema are common with these lesions.

Horowitz et al[7] studied five patients with epidermoid tumors and found that three tumors demonstrated high-signal intensity and two tumors low-signal intensity on T_1-weighted images. All five surgical specimens were analyzed using C-13 magnetic resonance imaging spectroscopy. Epidermoids with short T_1 values (white epidermoids) had negative CT values and high lipid content on magnetic resonance imaging spectroscopy. The predominant component was mixed triglycerides, but there was no significant amount of either free fatty acid or cholesterol. Epidermoids with long T_1 values (black epidermoids) had CT values approximating water, and exhibited a reduced lipid content on spectroscopy. Yuh et al[8] described two cases (one proved) of epidermoid tumor of the fourth ventricle; both were hypointense on T_1-weighted images and hyperintense on T_2-weighted images. Steffey et al[9] described five cases of intracranial epidermoid tumor, none of which occurred in the fourth ventricle. All five were hypointense on T_1-weighted images and hyperintense on T_2-weighted images.[9] Tampieri et al[10] described nine patients with epidermoid cysts (five proved), two of which were located within the fourth ventricle. Two of the nine cases were studied on a 0.5-T unit and the remaining seven on a 1.5-T system, but the authors did not indicate if the fourth ventricular tumors were studied on the 0.5- or the 1.5-T system.

Russell and Rubinstein[1] do not mention different characteristics of epidermoid tumors depending on their anatomical position within the brain or skull. One can assume that the signal characteristics of an epidermoid tumor within the fourth ventricle are the same as those of one within the cerebellopontine cistern. Those epidermoids within the diploe might have mixed-signal intensity depending on the amount of marrow fat within the tumor. Multiple cysts may be intermixed with desquamated epithelium. It is progressive desquamation that leads to slow expansion of the tumor. The differentiating feature between an epidermoid tumor and a dermoid tumor is the presence of skin appendages in the latter. Dermoid tumors contain hair follicles, sebaceous glands, and apocrine glands. The escape of the contents of a dermoid or epidermoid cyst into the cerebrospinal pathway can excite a granulomatous form of meningitis in which there is a foreign body giant cell reaction to particles, particularly the cholesterol granules.

In our series and in several others, the signal pattern has been low-signal intensity relative to brain parenchyma on T_1-weighted images (short repetition time; short echo time) and high-signal intensity on T_2-weighted images (long repetition time; long echo time). There is frequently a considerable cystic (water signal) component within these tumors that will produce low-signal intensity on T_1-weighted images. Cholesterol crystals should not produce high-signal intensity on T_1-weighted images. Sebaceous glands produce proteinaceous liquid that may show increased signal on T_1-weighted images. These glandular structures are present in dermoids and teratomas but not in epidermoids. We speculate that the signal characteristics of epidermoid tumors of the fourth ventricle show hypointensity on T_1-weighted images because the tumor is composed of desquamated squamous epithelium that contains keratin and because there is frequently a cystic (water) component. In addition, the outer layer of collagenous tissue should not produce high-signal intensity on T_1-weighted images.

Fourth ventricular epidermoid tumors are benign tumors that exert mass effect, have no peritumoral edema, and may be associated with hydrocephalus. At 0.5 T, they demonstrate decreased-signal intensity relative to brain parenchyma on T_1-weighted images and hyperintensity on T_2-weighted images.

References

1. Russell DS, Rubinstein LJ. *Pathology of Tumors of the Nervous System.* Baltimore, Md: Williams & Wilkins; 1989:690-695.

2. Chambers AA, Lukin RR, Tomsick TA. Cranial epidermoid tumors: diagnosis by computed tomography. *Neurosurgery.* 1977;1:276-280.

3. Davis KR, Roberson GH, Taveras JM, New PFJ, Trevor R. Diagnosis of epidermoid tumor by computed tomography. *Radiology.* 1976;119:347-353.

4. Fawcitt RA, Isherwood I. Radiodiagnosis of intracranial pearly tumors with particular reference to the value of computed tomography. *Neuroradiology.* 1976;11:235-242.

5. Mikhael MA, Mattar AG. Intracranial pearly tumors: the role of computed tomography, angiography and pneumoencephalography. *J Comput Assist Tomogr.* 1978;2:421-429.

6. Zimmerman RA, Bilaniuk LT, Dolinskas C. Cranial computed tomography of epidermoid and congenital fatty tumors of maldevelopmental origin. *CT.* 1979;3:40-50.

7. Horowitz BL, Chari MV, Reese J, Bryan RN. MR of intracranial epidermoid tumors: correlation of in-vivo imaging with in-vitro C-13 spectroscopy. *AJNR.* 1990;11:299-302.

8. Yuh WTC, Barloon TJ, Jacoby CG, Schultz DH. MR of fourth ventricular epidermoid tumors. *AJNR.* 1988;9:794-796.

9. Steffey DJ, De Filipp GJ, Spera T, Gabrielsen TO. MR imaging of primary epidermoid tumors. *J Comput Assist Tomogr.* 1988;12:438-440.

10. Tampieri D, Melanson D, Ethier R. MR imaging of epidermoid cysts. *AJNR.* 1989;10:351-356.

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NEUROLOGIST: Excellent opportunity for board-certified/board-eligible neurologists to join two existing neurologists in a stimulating, busy practice. Marquette General Hospital is a 321-bed regional referral center, with a comprehensive neurophysiology department and state-of-the-art technology that includes magnetic resonance imaging and CT scanning, and a hospital-based family practice residency. Medical students from Michigan State University's College of Human Medicine are regularly assigned to the hospital and offer an opportunity for teaching. Marquette General Hospital and its medical staff are committed to building a center of excellence in the neurosciences and have the necessary financial resources. The development of these services will require the leadership and cooperation of physicians in the field of neurology, neurosurgery, psychiatry, physical medicine and rehabilitation. Salaried and private practice positions are available. If this special opportunity is of interest to you, please send CV to: Robert J. Raica, Marquette General Hospital, 420 West Magnetic Street, Marquette, MI 49855.

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To join an associate neurlogy practice in south-central Nebraska. This opportunity comes with the full support of your colleages and offers exceptional life style and practice potential. Income guarantee, relocation, MP, office paid. Send CV or contact: Armando L. Frezza, President, Medical Support Services, 8806 Balcones Club Drive, Austin, TX 78750. Office (800) 288-7420; FAX (512) 331-6741.

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DOCTORS IN YOUR SPECIALTY are the best market for used/serviceable equipment that may be surplus to your needs. Advertise this equipment in an AMA specialty journal and reach your market. Call our "Classified Advertising" office toll free: National (800) 237-9851; in Florida (800) 553-8288.

NEUROLOGIST to join dynamic, midwest neurology group. This very busy practice is seeking an energetic neurologist with a strong interest in the clinical care of patients. This opportunity is located in a desirable, midwestern community abundant in cultural and sporting activities. The practice has a well-equipped radiology department with MRI and CT, and also, neurophysiology and neuropsychology departments. The appropriate candidate must be energetic, pleasant, BC/BE, with EMG experience. Please send curriculum vitae to: Box #814, c/o AON.

MAUI ORTHOPEDIC and Sports Medicine seeks neurologist to establish independent practice. Contact: William Gfeller, 450 Hookahi Street, Wailuku, Maui, HI 96793. (808) 244-5541.

Professional Opportunities

CHICAGO SUBURBAN solo practitioner with a busy practice seeking a full-time BC/BE clinical neurologist. EMG skills required. Immediate opening. Wonderful opportunity to expand with possible early partnership. Reply with CV to: Yvonne Jurcik, MD, 125 East Lake Cook Road, Buffalo Grove, IL 60089.

EXCELLENT OPPORTUNITY for BC/BE neurologist to join 80-physician, comprehensive, multi-specialty group in San Francisco Bay Area. Large, varied referral base from pediatrics, IM, FP, and surgery. EMG/NCV, EEG, evoked response testing, CT, MRI, radiology support all available on site. Opportunity to interface with sepcialists of all types including neurosurgeons. Major university teaching affiliation encouraged and possible. Close proximity to 400-bed full service, modern hospital serving population of 300,000. Competitive guaranteed salary with bonus productivity plan for initial 18 months leading to partnership track. Extensive benefit package including housing incentives. Unique cultural, recreational and educational opportunities. Send CV to: Gary D. Zweig, MD, Recruitment Chairman, Sunnyvale Medical Clinic, P.O. Box 3496, Sunnyvale, CA 94088-3496.

KANSAS — Board-certified, board-eligible neurologist to join child neurologist in rebuilding a three-person practice in the largest city in Kansas. Three large, well-equipped hospitals available for resident and undergraduate medical education. Located in clean, progressive community described as the franchise capital of the country. Competitive salary and benefits available. Send CV to: Richard C. Gilmartin, MD, 2620 East Central, Wichita, KS 67214.

NEUROLOGIST

Minneapolis/St. Paul — BC/BE adult neurologist wanted to join four other neurologists in a diverse practice consisting of both inpatient and outpatient settings. Group Health, Inc. is a non-profit, member governed HMO with one of the largest multi-specialty group practices in the Midwest. Our physicians are given the ability to focus on practicing high quality, cost-effective medicine in an environment that is relatively free of administrative duties. The Twin Cities are recognized as one of the best areas in the country to raise a family. The communities provide excellent schools, countless cultural events, numerous recreational activities, and a myriad of lakes and parks.

To inquire, please call: (612) 627-6122.
Or send CV to:

Group Health, Inc.
Attention: Ann Johnson
2829 University Avenue SE
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JULY 1991 — ASSOCIATE WANTED. Outstanding opportunity. $200K net probable by end of first year. Fully equipped neurologic institute. Only the best need apply. Send CV at once: Southeastern Neuroscience Institute, Inc., 5143 University Boulevard, West, Suite 3, Jacksonville, FL 32216-5939. (904) 733-0707; FAX (904) 730-9173.

THIRD NEUROLOGIST, BC/BE, desired for growing neurology practice in southern Michigan. EMG/EEG expertise and strong clinical skills required. Wide referral base. Equipped neurophysiological laboratory available. Exceptional lifestyle and cultural resources. Attractive salary and incentives leading to parternship in one year. Please write to: Neill S. Hirst, MD, 250 West Eisenhower Parkway, Suite 100, Ann Arbor, MI 48103. Or call: (313) 665-6638.

NEUROLOGIST

BC/BE neurologist wanted to join a busy neurology group in the northeastern region.

Situated in a beautiful summer/winter recreational area, in close proximity to several major cities.

This is an excellent professional opportunity in a rapidly growing community.

Highly competitive salary and fringe benefits with early partnership.

Please reply to:

Box #816, c/o AON

Professional Opportunities

CHICAGO — BC/BE neurologist to join existing practice. Highly motivated individual with strong clinical skills and EMG/EEG expertise needed to join two busy neurologists. Very strong medical school affiliation with teaching responsibilities for neurology and internal medicine, residents and medical students. Large referral base. Excellent benefit package. Please provide CV. Please contact: Box #818, c/o AON.

SEEKING ENERGETIC BE/BC NEUROLOGIST to join three adults and one child neurologist. Prefer someone with interest in general neurology and special interest and training in any of the following areas: sleep medicine, neurophysiology testing, neuro-rehabilitation, pain, or neuro-intensive care. Excellent medical community with all of the supportive consultants and technology. Send CV to: Neurological Associates of Grand Rapids, PC, 2855 Michigan Street, Northeast, Grand Rapids, MI 49506.

CHARLOTTE, NORTH CAROLINA: High quality group of six neurologists, all of whom are subspecialized, seeks to add a well-trained specialist. Contact: Mike Kaufman, MD, 126 Cottage Place, Charlotte, NC 28207. Or call: (704) 334-7311.

SOUTHEAST COAST — The Neuroscience Center of a 190-bed regional medical center is seeking a BC/BE neurologist to join in close association with their existing neurosurgeons. Exceptional medical facilities and neurological services including EEG/EMG, EP, CT, MRI. Excellent income guarantee plus benefits — large drawing area provides for outstanding potential. Located ninety minutes from one of this country's premiere seaside resorts, this dynamic community offers a quality lifestyle. Call Mark Prosperi at (800) 776-5776 for more details or send CV to: Cejka & Co., 1034 South Brentwood Boulevard, St. Louis, MO 63117.

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Professional Opportunities

EXPANDING, DYNAMIC ADULT neurology practice — BC/BE neurologist to join rapidly growing office and multi-hospital practice in New Jersey — 15 minutes from Manhattan. Candidate must be energetic and personable. EMG, EEG experience preferred. Send CV to: Joseph Sobelman, MD, 834 Avenue C, Bayonne, NJ 07002.

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NEUROLOGY

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Geisinger offers an excellent compensation package and a family-oriented lifestyle and easy access to New York City, Philadelphia, Pittsburgh, and Washington, D.C. Applicants should send CV to: **Anthony P. Turel, M.D., Director, Department of Neurology, Geisinger Medical Center, Danville, Pennsylvania 17822-1405.** Equal Opportunity Employer M/F/H/V.

Geisinger

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Well established neurology group in west New Orleans suburb, seeking recently trained, board-certified or board-admissable neurologist to join a very busy practice of clinical and hospital adult neurology.

Competitive salary and early partnership, in a superb practice setting with a pleasant lifestyle.

Send curriculum vitae to:

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FAX: (615) 395-4764

Professional Opportunities

EXCELLENT OPPORTUNITY for BC/BE neurologist to join 80-physician comprehensive, multi-specialty group in San Francisco Bay Area. Large, varied referral base from pediatrics, IM, FP, and surgery. EMG/NCV, EEG, Evoked Response Testing, CT, MRI, Radiology support all available on site. Opportunity to interface with specialists of all types including neurosurgeons. Major university teaching affiliation encouraged and possible. Close proximity to 400-bed full service, modern hospital serving population of 300,000. Competitive guaranteed salary with bonus productivity plan for initial 18 months leading to partnership track. Extensive benefit package including housing incentives. Unique cultural, recreational and educational opportunities. Send CV to: Gary D. Zweig, MD, Recruitment Chairman, Sunnyvale Medical Clinic, P.O. Box 3496, Sunnyvale, CA 94088-3496.

SOUTHEAST COAST — Pediatric Neurologist: Excellent quality of life available in Savannah-Hilton Head Area, site of the 1996 Olympic Games sailing events. Outstanding recreational opportunities, nation's largest urban Historic District, and superb symphony are among the attractions of living here. A well-trained, personable neurologist with special competence in child neurology is needed for a busy practice, currently consisting of two adult neurologists and one neurologist doing adult and child neurology, all with strong academic backgrounds. CT, EEG, EMG and physical therapy are available in-office with large hospital practice available in three hospitals, including a major regional teaching hospital, affiliated with the Medical College of Georgia. First year guarantee is $80,000 plus bonus, leading to full partnership after two years. Earnings potential, availability of strong multi-specialty support, and opportunities for teaching are extraordinary. If interested contact: Randy Wellman, Office Manager, Savannah Neurological Associates, PC, P.O. Box 23059, Savannah, GA 31403. (912) 354-8151.

— OHIO —

Very successful neurology group is seeking their third neurologist. Office conveniently located on the campus of a modern hospital located in a rapidly expanding suburb. This progressive city with its medical school and state university is an ideal place to satisfy both personal and professional needs. To learn more about this attractive opportunity we encourage you to call Barbara Lakoski at 1-800-243-4353 or send your CV to:

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ADULT NEUROLOGIST to associate with two separate, busy solo neurologists. Practices are referral based, with two separate offices and three voluntary hospitals. Successful candidate would be expected to develop a separate solo, but collaborative practice. Established physicians would expect to provide substantial support for beginning physician. Opportunity would provide for cross coverage and joint venturing of facilities. Successful candidate should have excellent clinical skills. The medical community has excellent neurophysiology, neuroradiology, and neurosurgery. Located in a medium size city with both excellent living conditions and an extremely solid economic base. Please contact: Jeffrey A. Ribner, MD, 503 Plaza Drive, Vestal, NY 13850. (607) 729-1521 or Robert R. Taylor, Jr., MD, 269 Riverside Drive, Johnson City, NY 13790. (607) 798-7143.

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SOUTHERN COLORADO: Exceptional practice and area. Opportunity to work with highly respected neurologist within a multi-specialty group. Practice to include: adult neurology, EEG, EMG, evoked potentials, CT and MRI. This vibrant community of 150,000 is located along the front range of the beautiful Rocky Mountains providing for a lifestyle second to none. Highly competitive first year income plus comprehensive benefits and relocation followed by partnership offering. For further details reply to: Wendy Perlman, 7385 Galloway Road, Miami, FL 33173. Or call: (800) 327-1585.

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COMPHEALTH provides the finest locum tenens (temporary physician staffing) service nationwide. Each CompHealth neurologist is carefully screened and referenced ensuring you competent, reliable coverage. Have your practice covered or join us and cover other practices. Call CompHealth, the nation's oldest and largest supplier of temporary physician staffing services at: (800) 328-3043 toll-free: in Utah (801) 264-6400. Or write: 4021 South 700 East, Salt Lake City, UT 84107.

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FACULTY POSITION — Available at Winthrop-University Hospital, a 548-bed major teaching affiliate of SUNY Stony Brook School of Medicine. Candidate should demonstrate excellence in patient care, teaching and research, as well as have an interest in pursuing a limited private practice. Expertise in EMG is desirable. Applicants should be board-certified/board-eligible. Interested applicants should send their curriculum vitae to: Malcolm H. Gottesman, MD, Acting Chief of Neurology, Winthrop-University Hospital, Division of Neurology, 222 Station Plaza North, Suite 438, Mineola, NY 11501. EOE. M/F/H/V.

CHIEF PEDIATRIC NEUROLOGY: A faculty position is available as Chief of the Division of Pediatric Neurology at the Nemours Children's Clinic. We are seeking an individual who is board-certified in pediatric neurology. In addition to direct patient care responsibility, the position offers academic appointment with the University of Florida at the level of Associate Professor/Professor. Guaranteed salary will be commensurate with applicant's experience. Please send CV to: Stephen Commins, MD, Chairman, Search Committee, Nemours Children's Clinic 807 Nira Street, Jacksonville, FL 32207. Academic status is offered by the University of Florida, an equal opportunity/affirmative action employer with whom Nemours is affiliated. Recruiting deadline: May 1, 1991.

ASSISTANT/ASSOCIATE PROFESSOR position — The Department of Neurology at the University of Minnesota Medical School has an opening for a tenure track Assistant/Associate Professor with subspecialty expertise in peripheral nerve and neuromuscular disease and in clinical electrophysiology. The candidate must have an MD, demonstrated ability to carry out peer-review funded independent research, and board-eligible in Neurology. The candidate will develop clinical care, training, and research programs in peripheral nerve disorders. Background should include fellowship in neuromuscular disease, training and board-eligibility/-certification in clinical neurophysiology with capability of directing a clinical laboratory, and a record of high-quality original publicaitons in peer-reviewed journals, etc. To be considered at the Associate Professor level, the candidate must show professional distinction in research and writing and demonstrated effectiveness in teaching and advising. This Assistant/Associate Professor will serve as an attending physician on the Neurology service and will participate in the teaching of residents, undergraduate, and graduate students. Applicants should send a CV by May 31, 1991 to: Richard W. Price, MD, Professor and Head, Deprtment of Neurology, Box 295, UMHC, Harvard Street at East River Road, Minneapolis, MN 55455. The University of Minnesota is an equal opportunity employer and specifically invites and encourages applications from women and minorities.

Neurologist

The Mason City Clinic
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the Heartland.

We are looking for a neurologist to join our very busy practice. Small-town security within two hours of Minneappolis and Des Moines.

MRI, CT, sleep lab, EEG, EMG, neurosurgery, cardiac surgery, orthopedic surgery, cancer center, GI lab, and ENT capabilities.

Excellent salary
and benefits.

Submit CV to:

Ralph A. Wolf, Administrator
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(515) 423-2435

IMMEDIATE OPENING FOR A

GENERAL NEUROLOGIST

Private practice opportunity available immediately in east Tennessee with a well established neurologic practice.

Candidate should be BE/BC with competence in EEG, EMG and evoked potentials. Compensation individually negotiable. Excellent benefits also included. There is a wide variety of recreational facilities also available in the area.

Please submit CV to:

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Baptist Professional
Building
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The neurosurgeons currently have a large volume of surgery cases (only 10% trauma) at St. Marys Hospital, a 340-bed facility located five blocks from the clinic. Ideal candidate should have interest in general and vascular neurosurgery, and desire a long term commitment to Dean Medical Center. All candidates must be board-eligible with goals to become board-certified.

Competitive salary and benefits provided with this position. For more information, send CV to or contact:

Scott M. Lindblom
Dean Medical Center
1313 Fish Hatchery Road
Madison, WI 53715

Work: (608) 252-8022
or
Home: (608) 276-8989

Faculty Positions

LOYOLA UNIVERSITY Chicago Stritch School of Medicine, Department of Neurology invites applications for two positions at the assistant professor level. Applicants should be board-eligible or -certified in neurology and have subspecialty expertise in either epilepsy, movement disorders, cerebrovascular or neuromuscular diseases. Preference will be given to candidates with clinical research interests. Send CV to: Gastone Celesia, MD, Chairman, Neurology Department, Loyola University Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola University Chicago is an equal opportunity/affirmative action employer.

Fellowships

CEREBROVASCULAR FELLOWSHIP available in Department of Neurology at the University of New Mexico. Individual will participate in clinical drug trials and research involving spect ¹H-NMR spectroscopy, MRI angiography and magnetoencephalography. Contact: Gary Rosenberg, MD, University of New Mexico Medical Center, Department of Neurology, Albuquerque, NM 87131-5281. (505) 277-3342. EEO.

Residencies

NEUROLOGY RESIDENCY PGY-2 position Stanford University — An unexpected neurology residency position is available starting July, 1991 at Stanford University Medical Center. For further information, contact: Dr. Gregory W. Albers, Director, Residency Training Program, Department of Neurology and Neurological Sciences, Stanford University Medical Center, Stanford, CA 94305. Equal opportunity employer.

SECOND YEAR NEUROLOGY RESIDENCY — Opening July 1991 for PGY3 resident in Georgetown University Program. Send CV to: Jonathan H. Pincus, MD, Professor and Chairman, Georgetown University Hospital, Department of Neurology, 1 Bles Building, 3800 Reservoir Road, NW, Washington, DC 20007. (202) 784-2170. EOE.

Residencies

THE UNIVERSITY OF CHICAGO Neurology Department is offering a second year neurology residency position (PGY 3) beginning July 1991. For information contact: Richard P. Kraig, PhD, MD, Residency Director, Department of Neurology, University of Chicago Medical Center, 5841 South Maryland, BH - Box 425, Chicago, IL 60637. (312) 702-0151.

THE UNIVERSITY OF CINCINNATI Neurology Department is offering a second year neurology residency position (PGY3) beginning as soon as possible. For information contact: Joseph P. Broderick, MD, Residency Director, Department of Neurology, University of Cincinnati Medical Center, Cincinnati, OH 45267-0525. (513) 558-5431.

Medical Equipment/Supplies

SOLO PHYSICIAN joining group has used equipment in good condition for sale; Nicolet Evoked Potential, EMG, Oxford Ambulatory EEG (scanner, recorder, sleep stages), Biosound Carotid Ultrasound Imager. Contact: Paul Bustion, MD, 1801 North Senate Boulevard, Suite 510, Indianapolis, IN 46202. (317) 929-5828.

FOR SALE — BIOLOGIC III

20 channel EEG/VER; color jet printer; 80286 16 bit microprocessor. 5¼" dbl/dbl floppy with 1.2 MEG storage; 20 MEG hard disk; RGB 13" CRT. Cart, banker. $50,000 OBO.

Contact Barbara Jessen: (206) 242-0201.

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Cognitive Neuroscience Section • Medical Neurology Branch

National Institute of Neurological Disorders and Stroke
National Institutes of Health • Public Health Service

Starting Date: Summer or Fall, 1991

We are seeking psychologists with a strong interest in either memory and amnesia, reasoning and problem solving, social cognition or cognitive event-related potentials. Exceptional candidates with other areas of interest will be considered. The Research Fellow positions will be in the Cognitive Neuroscience Section of the Medical Neurology Branch, NINDS, NIH. The Cognitive Neuroscience Section conducts research in the following areas: *Memory and Amnesia, Neurolinguistics and Aphasia, Visual Attention, Perception and Agnosia, Cognitive Psychophysiology, Frontal Lobe Functions, and Knowledge Representation* using cognitive science, neuropsychological and evoked-response techniques. A variety of normal control and patient populations are being studied including Stroke, Parkinson's Disease, Cerebellar lesions, Alzheimer's Disease, Encephalitis, Demyelinating Disorders, HIV Dementia, Brain Tumors, Head Injury, Multiple Personality Disorder, Chronic Fatigue Syndrome, Dystonia, and Progressive Supranuclear Palsy. The ability to conduct original research, as well as engage in collaborative research, is required. Candidates trained in cognitive science/psychology programs are encouraged to apply.

The Cognitive Neuroscience Fellowships *include* tutorial training in neurobehavioral assessment and diagnostics, participation in clinical rounds, development of research projects, and seminar presentations. The training program is oriented towards developing skills and credentials for a career in cognitive neuropsychology. As a Research Fellow, your salary will range from $24,000 to $40,345 depending on experience and qualifications. Travel expenses and Federal health care benefits are available.

For further information, please contact:

Jordan Grafman, Ph.D., Chief
Cognitive Neuroscience Section
Medical Neurology Branch
NINDS, NIH
Building 10, Room 5C422
9000 Rockville Pike
Bethesda, Maryland 20892
(Phone: 301-496-0220)

Interested candidates should send a vitae, statement of research interests, representative reprints or pre-prints, and three letters of recommendation to Dr. Grafman. For further information and qualification requirements contact **Glenn Hartzoge, NINDS Personnel Office, (301) 496-6334.**

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Behavioral Neurology Fellowship

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Starting Date: July 1, 1991

We are awarding a Behavioral Neurology Fellowship beginning July, 1991. We are seeking a Board Certified or eligible neurologist with a strong research interest in the brain mechanisms underlying cognitive functioning. The Clinical Associate position will be in the Cognitive Neuroscience Section of the Medical Neurology Branch, NINDS, NIH. The Cognitive Neuroscience Section conducts research in the following areas: *Memory and Amnesia, Neurolinguistics and Aphasia, Visual Attention, Perception and Agnosia, Cognitive Psychophysiology, Frontal Lobe Functions, and Knowledge Representation* using neuropsychological and evoked-response techniques. A variety of patient populations are studied including Stroke, Parkinson's Disease, Cerebellar lesions, Alzheimer's Disease, Encephalitis, Demyelinating Disorders, HIV Dementia, Brain Tumors, Head Injury, Multiple Personality Disorder, Chronic Fatigue Syndrome, Dystonia, and Progressive Supranuclear Palsy. The initiation of experimental pharmacological intervention studies in patients suffering from memory impairment is encouraged.

The Behavioral Neurology Fellowship *includes* tutorial training in neurobehavioral assessment and diagnostics, participation in clinical rounds, development of research projects, and seminar presentations. The training program is oriented towards developing skills and credentials for a career in academic neurology. Clinical Associates receive an initial salary of $37,000 a year. Moving expenses, travel expenses and Federal health care benefits are available.

For further information, please contact:

Jordan Grafman, Ph.D., Chief
Cognitive Neuroscience Section
Medical Neurology Branch
NINDS, NIH
Building 10, Room 5C422,
9000 Rockville Pike
Bethesda, Maryland 20892
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Please see following page for brief summary of prescribing information.

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Cafergot®

(ergotamine tartrate and caffeine) tablets, USP
(ergotamine tartrate and caffeine) suppositories, USP

DESCRIPTION

Cafergot® (ergotamine tartrate and caffeine) Tablet

ergotamine tartrate USP .... 1 mg
caffeine USP .... 100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

Cafergot® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP .... 2 mg
caffeine USP .... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

Cafergot® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

ACTIONS: Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS

Cafergot® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

PRECAUTIONS: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

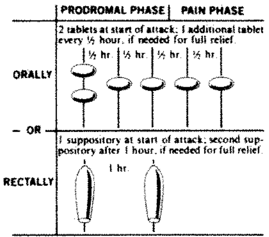
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief.
½ hr.
½ hr.
½ hr.
½ hr.
ORALLY
— OR —
1 suppository at start of attack; second suppository after 1 hour, if needed for full relief.
1 hr.
RECTALLY

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE: The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

HOW SUPPLIED

Cafergot® (ergotamine tartrate and caffeine) Tablets

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Dilantin® KAPSEALS® (Extended Phenytoin Sodium Capsules, USP)

Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

Dilantin® Kapseals®

(extended phenytoin sodium capsules, USP)

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebellar dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Dose reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persist, termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance of adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinical condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without first seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize the development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optimal dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels or which phenytoin may affect. Serum level determinations for phenytoin are especially helpful when possible drug interactions are suspected. The most commonly occurring drug interactions are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcohol intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfiram, estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazines, phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abuse, reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium ions which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antacid preparations containing calcium should be staggered in patients with low serum phenytoin levels to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbital, sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valproic acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures in susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenytoin include: corticosteroids, coumarin anticoagulants, digitoxin, doxycycline, estrogens, furosemide, oral contraceptives, quinidine, rifampin, theophylline, vitamin D.

Drug/Laboratory Test Interactions: Phenytoin may cause decreased serum levels of protein-bound iodine (PBI). It may also produce lower than normal values for dexamethasone or metyrapone tests. Phenytoin may cause increased serum levels of glucose, alkaline phosphatase, and gamma glutamyl transpeptidase (GGT).

Carcinogenesis: See "Warnings" section for information on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug because phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountered with phenytoin therapy are referable to this system and are usually dose-related. These include nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizziness, insomnia, transient nervousness, motor twitchings, and headaches have also been observed. There have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, tremor and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receiving long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever have included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the most common; other types of dermatitis are seen more rarely. Other more serious forms which may be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens-Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reported in association with administration of phenytoin. These have included thrombocytopenia, leukopenia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow suppression. While macrocytosis and megaloblastic anemia have occurred, these conditions usually respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingival hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptoms such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemic lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimated to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may become comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 30 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, but as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As much as 25 times the therapeutic dose has been taken to result in a serum concentration over 100 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed and appropriate supportive measures employed. Hemodialysis can be considered since phenytoin is not completely bound to plasma proteins. Total exchange transfusion has been used in the treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should be borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G280

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Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

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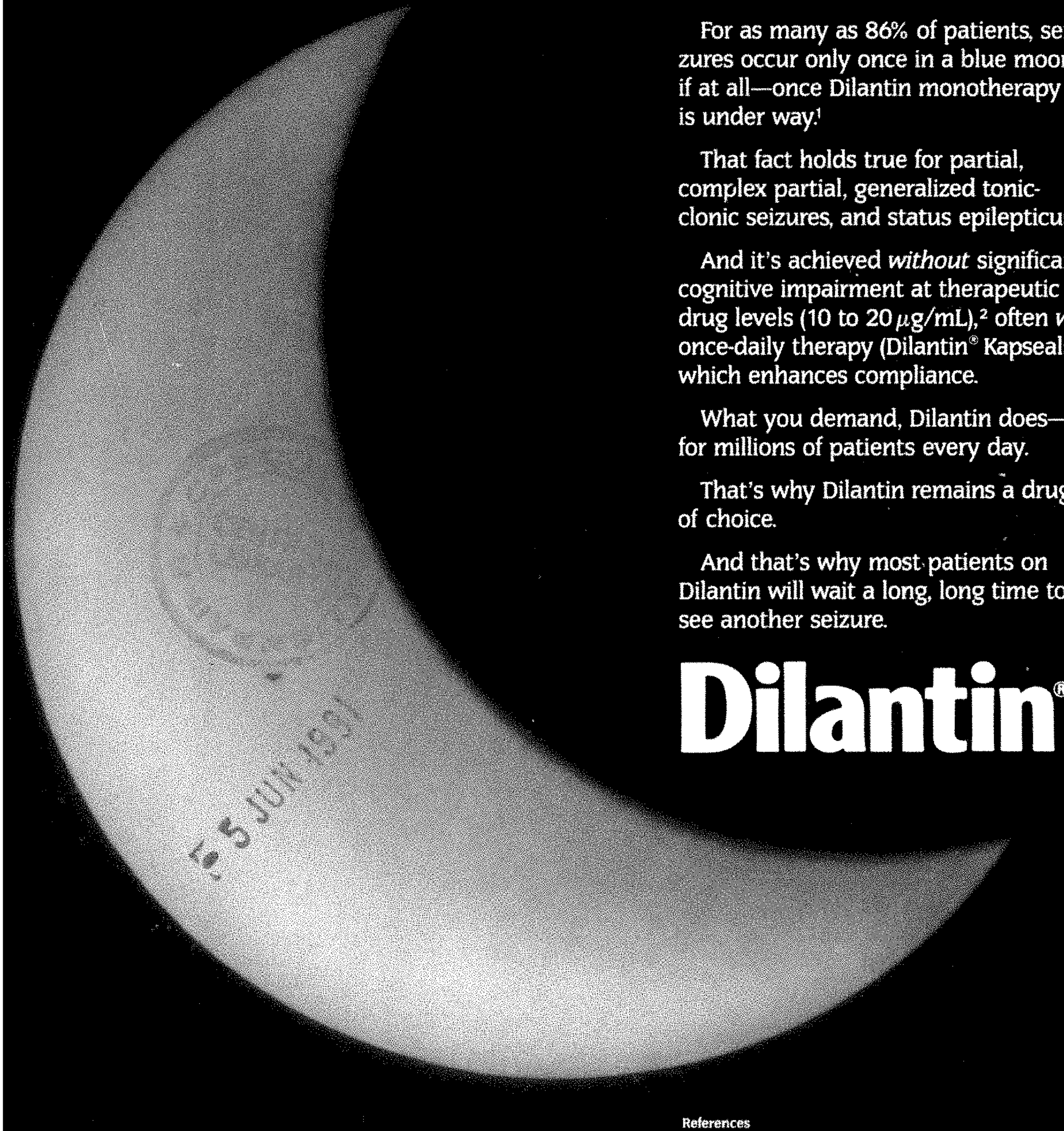

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That fact holds true for partial, complex partial, generalized tonic-clonic seizures, and status epilepticus.

And it's achieved *without* significant cognitive impairment at therapeutic drug levels (10 to 20 μg/mL),[2] often *with* once-daily therapy (Dilantin® Kapseals®), which enhances compliance.

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Dilantin®

"Once in a blue moon" describes the phenomenon in which the moon appears as a brilliant blue. Seen worldwide following the volcanic eruption of Krakatoa in 1883, the blue moon occurs only when atmospheric cloud droplets, each less than 5 μm in diameter, form in abundance—an exceedingly rare event.[3]

References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976; 31:292-296.

Please see adjacent page for brief summary of prescribing information.

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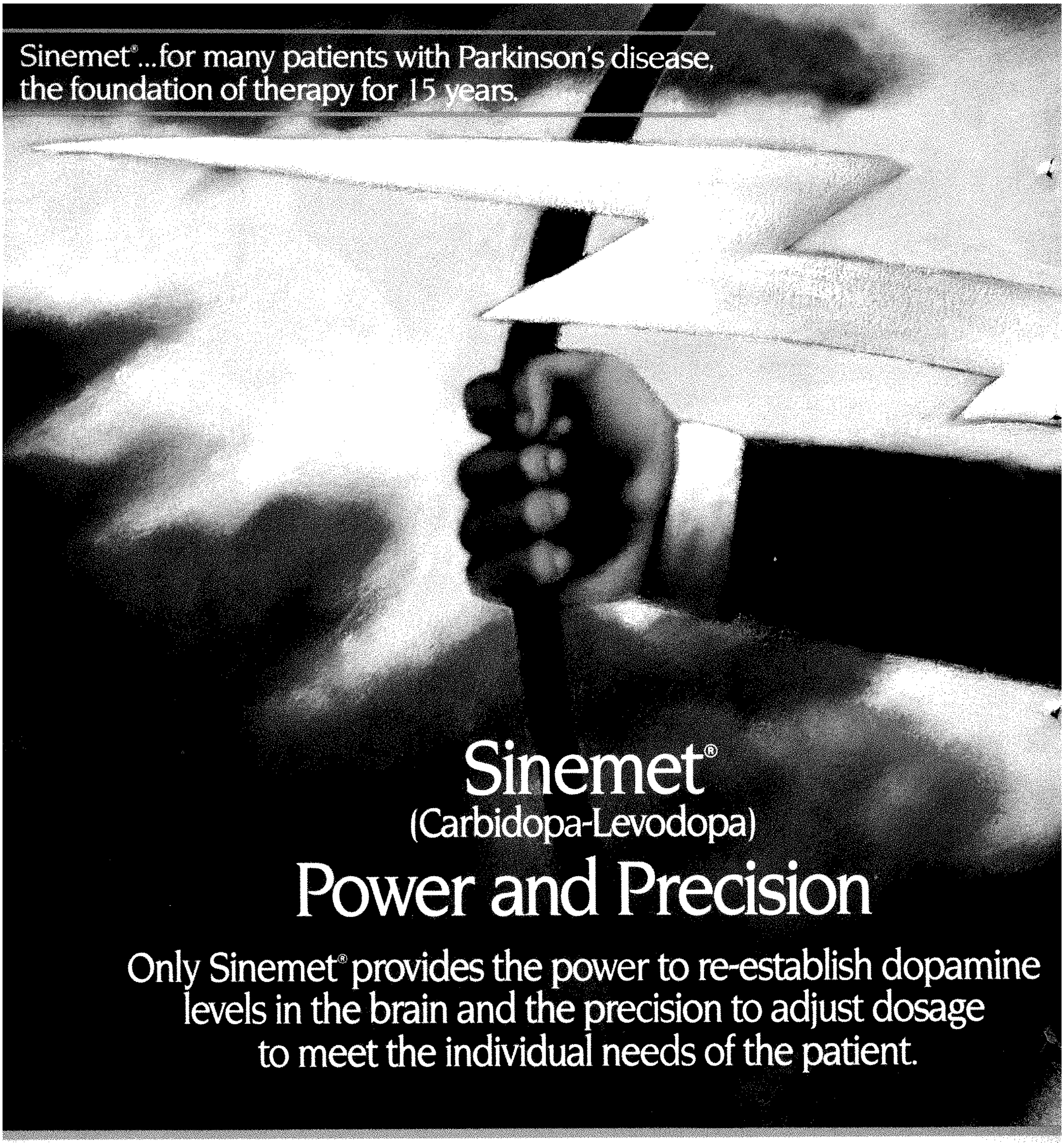

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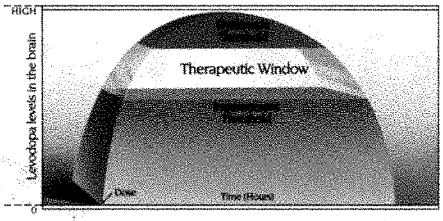

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Dopamine replacement is the mainstay of therapy in Parkinson's disease. And, only Sinemet® has the power to re-establish dopamine levels in the brain.

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Nothing else gives you this power and precision to manage the signs and symptoms of Parkinson's disease like Sinemet®.

As with levodopa, SINEMET* may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine levels following administration of levodopa.

Please see a brief summary of prescribing information on the adjoining page.

Sinemet®
(Carbidopa-Levodopa)

ONE OF A KIND

DU PONT
PHARMA

Du Pont Pharmaceuticals
Wilmington, DE 19880-0026

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For many patients with Parkinson's disease

Dosage Guidelines

*Individualized dosage—a key to clinical success with Sinemet**

- Begin when symptoms first interfere with normal function
- Adjust as necessary to help maintain relief of symptoms

1

For initial therapy...Start with:

SINEMET 25-100

containing 25 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

one tablet t.i.d.

If necessary, to control symptoms, dosage may be increased by one tablet every day or every other day until a dosage of eight tablets of Sinemet 25-100 a day is reached.

2

When it is evident that patients need more levodopa...Transfer to:

SINEMET 25-250

containing 25 mg carbidopa (anhydrous equivalent) and 250 mg levodopa

one tablet t.i.d.

If still more levodopa is necessary, dosage with Sinemet 25-250 may be increased by one-half to one tablet every day or every other day to a maximum of eight tablets a day.

3

When individualizing dosage...Titrate with:

SINEMET 10-100

containing 10 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

or SINEMET 25-100

or SINEMET 25-250

The optimum daily dosage of Sinemet must be determined by careful titration in each patient. Tablets of the three strengths may be given separately or combined as needed to provide the optimum daily dosage.

For patients transferred from levodopa

DISCONTINUE LEVODOPA AT LEAST 8 HOURS BEFORE STARTING SINEMET.

The starting dose for Sinemet should provide about 25 percent of previous levodopa requirements. (Patients receiving less than 1500 mg of levodopa a day should be started on one tablet of Sinemet 25-100 t.i.d. or q.i.d.)

Sinemet®
(Carbidopa-Levodopa)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa*. Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System*: ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric*: confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal*: dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic*: weight gain or loss, edema. *Integumentary*: malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary*: urinary retention, urinary incontinence, dark urine, priapism. *Special Senses*: diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous*: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

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DIV OF MERCK & CO., INC.,
WEST POINT, PA 19486, USA

FOR:

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PHARMA

Du Pont Pharmaceuticals
Wilmington, DE 19880-0026

Brief Summary of 6219/7667300

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ARCHIVES
OF
Neurology

Vol 48 **No. 5** **MAY 1991**

BOOKS

Neonatal Seizures 465
Claude G. Wasterlain, Paul Vert, (eds),
Reviewed by Fritz E. Dreifuss, MB, FRCP, FRACP, Charlottesville, Va

Amyotrophic Lateral Sclerosis. Concepts in Pathogenesis and Etiology 465
Arthur J. Hudson, (ed),
Reviewed by David Goldblatt, MD, Rochester, NY

Imaging of the Nervous System 465
Paul Butler, Reviewed by Stephen E. Joy, MD, Rochester, NY

Essentials of Child Neurology 466
Suresh Kotagal, Reviewed by James F. Bale, Jr, MD, Iowa City, Iowa

Delirium: Acute Confusional States 466
Z. J. Lipowski, Reviewed by Andrew Kertesz, MD, London, Ontario

Lesion Analysis in Neuropsychology 467
Hanna Damasio, Antonio R. Damasio,
Reviewed by Robert J. Joynt, MD, PhD, Rochester, NY

LETTERS TO THE EDITOR

Magnetic Resonance Imaging Hyperintensities in Alzheimer's Disease 468
William M. McDonald, MD; P. Murali Doraiswamy, MD;
K. Ranga R. Krishnan, MD, Durham, NC

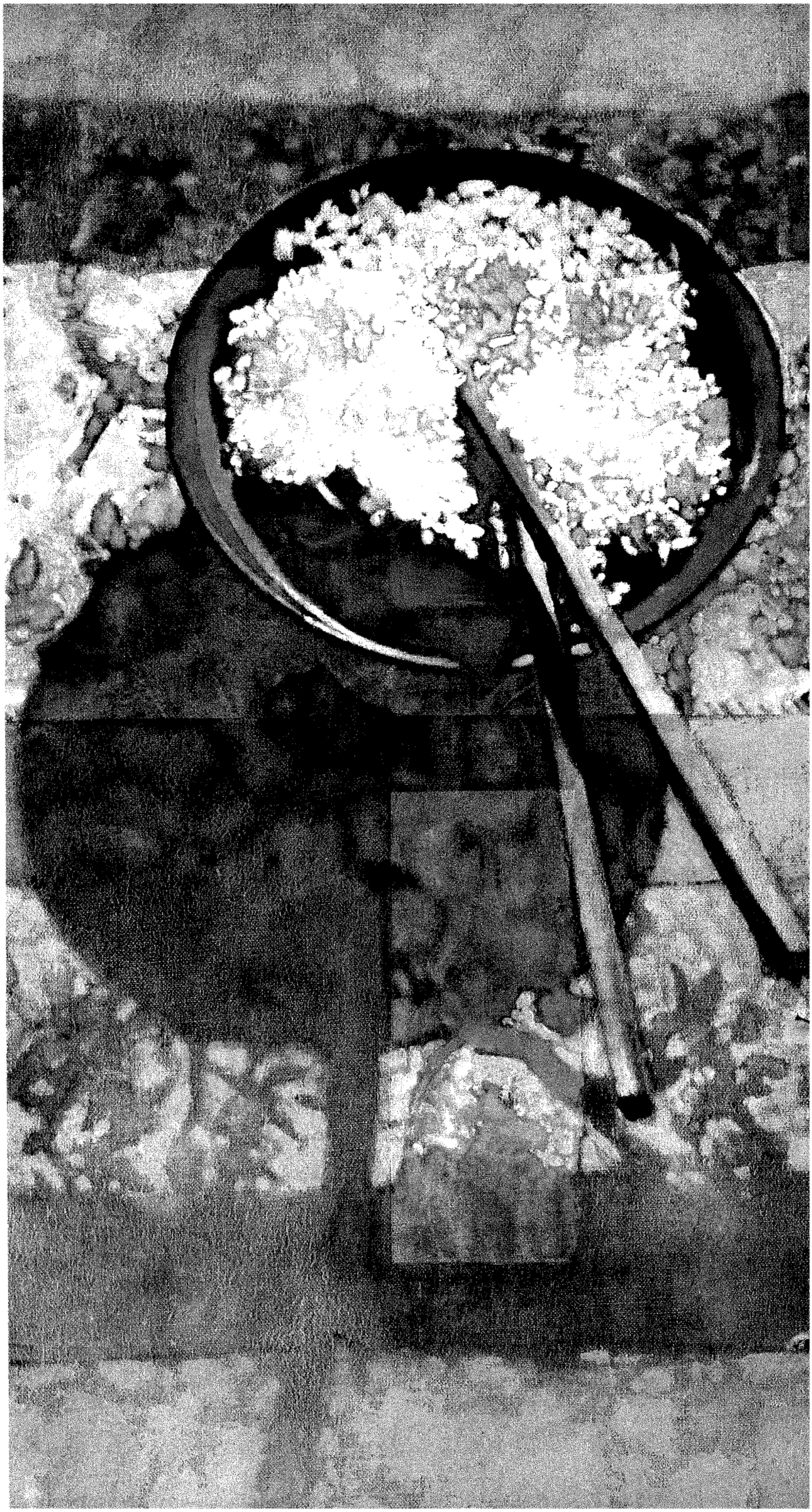
Franz Fazekas, MD; Reinhold Schmidt, MD; 468
Hans Offenbacher, MD, Graz, Austria;
John B. Chawluk, MD, Pottsville, Pa;
Abass Alavi, MD, Philadelphia, Pa

In Reply
Didier Leys, MD; Marc Steinling, MD; Jean-Pierre Pruvo, MD;
Henri Petit, MD, Lille, France; Philip Scheltens, MD,
Frederik Barkhof, MD, Amsterdam, the Netherlands

Continued on page 455.

TRIGGERS MIGRAINE*

激發偏頭痛



ABORTS MIGRAINE

抑制偏頭痛

Cafergot®

(ergotamine tartrate and caffeine) Tablets/Suppositories

- Highly Effective:
  Aborts migraines before they start
  Stops migraines in progress
- Reliable and Predictable

The choice from the start

*MSG, a common additive in Chinese cooking, may precipitate migraine attacks in susceptible individuals.

Please see following page for brief summary of prescribing information.

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

C-CAF-0689-01

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Cafergot®

(ergotamine tartrate and caffeine) tablets, USP
(ergotamine tartrate and caffeine) suppositories, USP

DESCRIPTION

Cafergot® (ergotamine tartrate and caffeine) Tablet

ergotamine tartrate USP .... 1 mg
caffeine USP .... 100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

Cafergot® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP .... 2 mg
caffeine USP .... 100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

Cafergot® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

ACTIONS: Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS

Cafergot® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

PRECAUTIONS: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

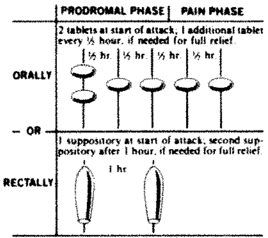
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief.
½ hr.
½ hr.
½ hr.
½ hr.
ORALLY
— OR —
1 suppository at start of attack; second suppository after 1 hour, if needed for full relief.
1 hr
RECTALLY

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE: The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

HOW SUPPLIED

Cafergot® (ergotamine tartrate and caffeine) Tablets

Shell pink colored, sugar coated, imprinted "CAFERGOT" on one side, "S" on other side. Bottles of 250, NDC 0078-0034-28, and cartons of three SigPak® (dispensing unit) packages, each containing 30 tablets in individual blisters, NDC 0078-0034-42.

Cafergot® (ergotamine tartrate and caffeine) Suppositories

Sealed in fuchsia-colored aluminum foil, imprinted "S CAFERGOT® SUPPOSITORY 78-33 SANDOZ". Boxes of 12, NDC 0078-0033-02.

[DECEMBER 1, 1990 CAF-Z26]

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INDEX TO ADVERTISERS

Berlex Imaging	456A-D
Ciba Pharmaceutical Company	459-460
Du Pont Pharmaceuticals	Cover 2-450
Gate Pharmaceuticals	537-538
Geigy Pharmaceuticals	464A-B
GenDerm Corporation	517-518
Eli Lilly & Company	512A-D
Miles Pharmaceuticals	498-500
Parke-Davis	Cover 3-Cover 4
Sandoz Pharmaceuticals	452-454, 462-464, 535-536

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AMP

ARCHIVES

Third-Nerve Palsies and Angiography 470
James R. Keane, MD, Jamshid Ahmadi, MD, Los Angeles, Calif

Editorial

Freeze the Ocean 471
Robert J. Joynt, MD, PhD, Rochester, NY

SPECIAL ARTICLES

Caring for the Underserved: Health Insurance Coverage Is Not Enough 472
Matthew Menken, MD, New Brunswick, NJ

Access to Health Care: One Neurologist's Perspective 476
Michael P. Earnest, MD, Denver, Colo

Access to Neurological Care for Minorities 480
Edgar J. Kenton, MD, Philadelphia, Pa

ORIGINAL CONTRIBUTIONS

Clinical Evaluation of Stenosis of the Carotid Bifurcation With Magnetic Resonance Angiographic Techniques 484
Daniel K. Kido, MD, Robert J. Panzer, MD, Rochester, NY;
Jerzy Szumowski, PhD, Portland, Ore; Joshua Hollander, MD;
Leena M. Ketonen, MD, PhD; Ahmad Monajati, MD;
Kenneth Ouriel, MD; James V. Manzione, MD, DMD, Rochester, NY;
Charles L. Dumoulin, PhD; Steven P. Souza, PhD, Schenectady, NY;
Jill L. Katz, RN, Barbara M. Rothenberg, MPA, MA, Rochester, NY

Delayed Visual Loss due to Trauma of the Internal Carotid Artery 490
Joel M. Weinstein, MD; Daniel A. Rufenacht, MD;
Curtis R. Partington, MD, PhD; Virgil B. Graves, MD;
Charles M. Strother, MD; Richard E. Appen, MD;
Daniel M. Jacobson, MD, Madison, Wis;
Terry A. Cox, MD, Vancouver, British Columbia;
Mark L. Moster, MD, Philadelphia, Pa

Acute Pseudobulbar or Suprabulbar Palsy 501
G. Besson, MD; J. Bogousslavsky, MD; F. Regli, MD;
P. Maeder, MD, Lausanne, Switzerland

Regional Cerebral Blood Flow in Developmental Stutterers 509
Kenneth D. Pool, MD; Michael D. Devous, Sr, PhD;
Frances J. Freeman, PhD; Ben C. Watson, PhD;
Terese Finitzo, PhD, Dallas, Tex

Glutethimide Treatment of Disabling Action Tremor in Patients With Multiple Sclerosis and Traumatic Brain Injury 513
Mindy L. Aisen, MD, Mary Holzer, MS, OTR, White Plains, NY;
Michael Rosen, PhD, Cambridge, Mass; Mark Dietz, MD, Denver, Colo;
Fletcher McDowell, MD, White Plains, NY

Continued on page 456.

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ARCHIVES

Familial Inclusion Body Myositis Among Kurdish-Iranian Jews 519
Roberto Massa, MD; Boaz Weller, MD; George Karpati, MD;
Eric Shoubridge, PhD; Stirling Carpenter, MD, Montreal, Quebec

Altered Cutaneous Sensation in Trigeminal Neuralgia 523
Turo J. Nurmikko, MD, Tampere, Finland

Neurophysiologic Studies of the Peripheral Nervous System in Nephropathic Cystinosis 528
Michael R. Swenson, MD; Steve Rimmer, MD;
Jerry A. Schneider, MD; Ronald B. Melles, MD;
Doris A. Trauner, MD, San Diego, Calif;
Barrett Katz, MD, San Francisco, Calif

Clinical Issues Relating to the Diagnosis of Mild Dementia in a British Community Survey 530
Daniel W. O'Connor, MD; Penelope A. Pollitt, PhD;
John B. Hyde, MRCPsych; Nigel D. Miller, MRCPsych;
Janet L. Fellowes, MRCPsych, Cambridge, United Kingdom

Cerebral Structure on Magnetic Resonance Imaging in Language- and Learning-Impaired Children 539
Terry L. Jernigan, PhD; John R. Hesselink, MD;
Elizabeth Sowell, San Diego, Calif;
Paula A. Tallal, PhD, New Brunswick, NJ

HISTORY OF NEUROLOGY

***Allochiria* vs *Allesthesia*: Is There a Misperception?** 546
Kimford J. Meador, MD; Martha E. Allen, MD; Robert J. Adams, MD;
David W. Loring, PhD, Augusta, Ga

OBSERVATION

Germ Cell Tumors Masquerading as Central Nervous System Sarcoidosis 554
David M. Peeples, MD; Barney J. Stern, MD;
Violet Jiji, MD, Baltimore, Md;
K. Singh Sahni, MD, Richmond, Va

REGULAR DEPARTMENTS

Calendar 457

News 458

Instructions for Authors 461

Index to Advertisers 454

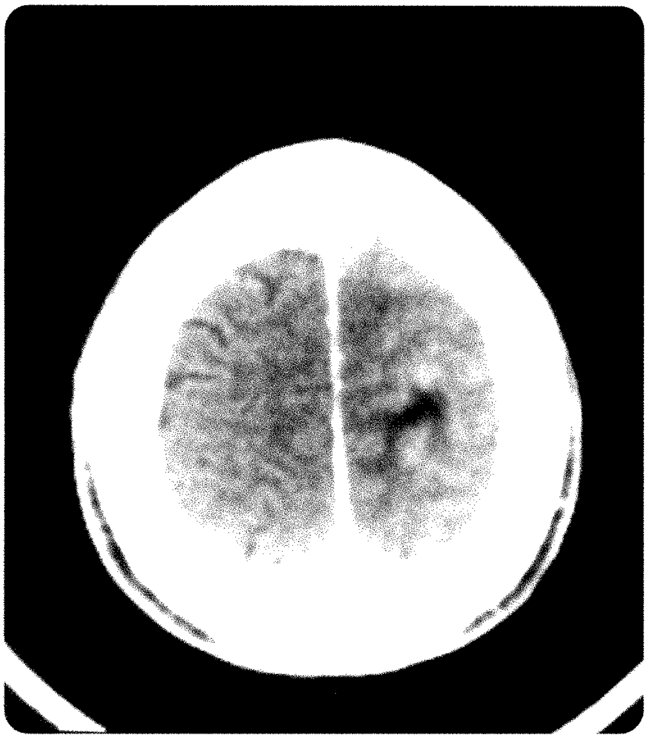
Classified Advertising 550

THE DECISION IS YOURS.

COMPARE.

THE CASE: A 40-year-old man presented with a 2-month history of involuntary muscle contractions of the right arm and mild weakness of the left leg.

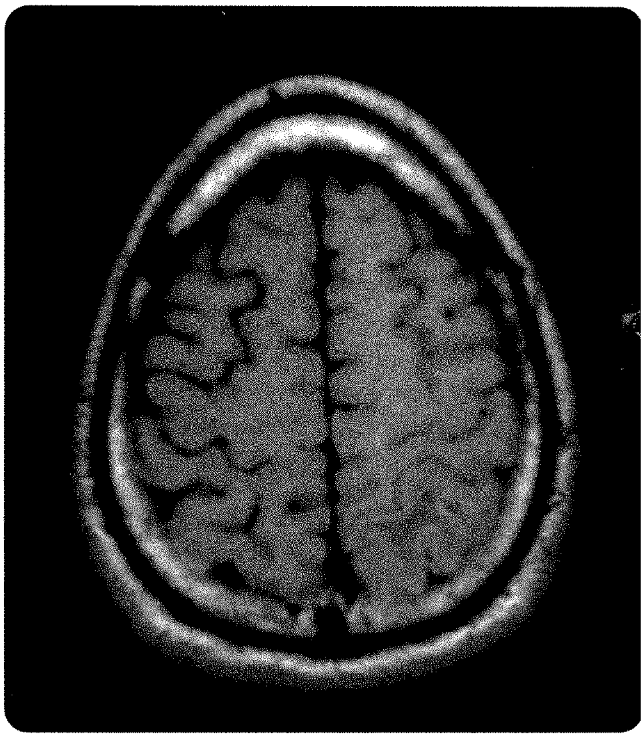
First there was CT.



Contrast CT scan shows an area of low attenuation in the left parietal lobe. A questionable focus of contrast is seen, but this may represent cerebral cortex.

Images courtesy of Michael R. Ross, MD, Stanford University Medical Center, Stanford, California

Then MRI.



T1-weighted (TR 800/TE 20) unenhanced MR image, obtained with a 1.5-T imager, shows subcortical hypointensity in the left posterior parietal lobe. The surrounding sulci appear to be compressed, but a mass is not clearly appreciated.

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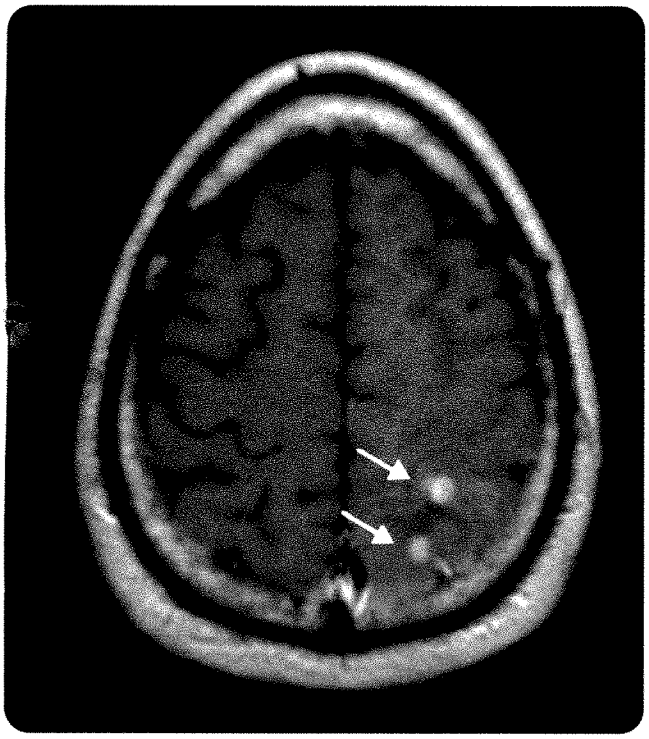
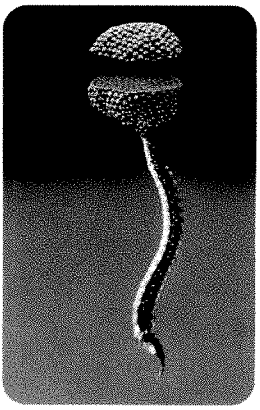
AND CONTRAST.

Now, *Magnevist*®-enhanced MRI lets you see even more.



T1-weighted (TR 800/TE 20) image enhanced with MAGNEVIST® injection reveals two discrete nodules (arrows). This nodular enhancement is highly suggestive of a primary brain tumor, which was confirmed upon biopsy to be an astrocytoma.



Magnevist®

(gadopentetate dimeglumine 469.01 mg/mL)

INJECTION

NOTHING LOCATES LESIONS BETTER

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.

Well tolerated[1] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCE: 1. Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 μg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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Berlex Laboratories, Inc.
Wayne, New Jersey 07470
60621-6 Revised 7/90 90-890-0068 2/91

BERLEX IMAGING®

Calendar

CALENDAR OF MEETINGS

1991		
May	6-8	"Neurotoxins and Their Potential Role in Neurodegeneration," Adams Mark Hotel, Philadelphia, Pa. Contact Marketing Department, The New York Academy of Sciences, 2 E 63rd St, New York, NY 10021; (212) 838-0230.
	7-10	Ecuadoran Society of Neurology, Quito, Ecuador. Contact Ecuadoran Society of Neurology, PO Box 2821, Quito, Ecuador.
	15-18	Meeting of the Neurosurgical Society of America, San Destin Beach Hotel, San Destin, Fla. Contact Russell W. Hardy, MD, Secretary, Neurosurgical Society of America, 2074 Abington Rd, Cleveland, OH 44106; (216) 844-3004.
	16-18	"Neurosurgical/Neurological Intensive Care: Update and Review," The Cleveland (Ohio) Clinic Foundation. Contact The Cleveland Clinic Foundation, Department of Continuing Education, 9500 Euclid Ave, Room TT-31, Cleveland, OH 44195-5241; 1-800-762-8173.
	17-18	"Pediatric Neurology for the '90's," Wilmington, Del. Contact Jeanne Cole, Continuing Medical Education Office, Alfred I. duPont Institute, 1600 Rockland Rd, Wilmington, DE 19899; (302) 651-6753.
	27-29	New Frontiers on Acute Ischemic Stroke—An Update, Rome, Italy. Contact Stroke Secretariat, Via Bertolini, 26/B, 00197 Rome, Italy.
	30-June 1	International Conference on Stroke, Geneva, Switzerland. Contact N. M. Bornstein, MD, International Conference on Stroke, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211 Geneva, Switzerland.
June	1-6	The 15th International Symposium on Cerebral Blood Flow and Metabolism, James L. Knight International Center, Miami, Fla. Contact Ms Jenny Bernal, Conference Coordinator, Brain '91, University of Miami Conference Center, 400 SE Second Ave, Fourth Floor, Miami, FL 33131.
	2-6	Ninth International Congress of Electromyography, Jerusalem, Israel. Contact Dr Arieh N. Gilai, Convener, EMG-CN-IX Congress, PO Box 29334, Tel Aviv 61292, Israel.
	5-7	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," Schuss Mountain Resort, Mancelona, Mich. Contact Susan Mitchell, EdD, 2929 Race St, Fort Worth, TX 76111; (817) 831-2604.
	7	"Neuro-Ophthalmology 1991," Cleveland, Ohio. Contact John Rus, Office of Continuing Medical Education, 2109 Adelbert Rd, W-175, Cleveland, OH 44106; (216) 368-2409.
	10-13	Twelfth Annual Child Neurology Postgraduate Course, Sonesta Beach Hotel, Key Biscayne, Fla. Contact Oscar Papazian, MD, Department of Neurology, Miami Children's Hospital, 3200 SW 60th Ct, Miami, FL 33155; (305) 662-8330.
	16-21	Seventh International Conference on the Acquired Immunodeficiency Syndrome, Florence, Italy. Contact Christina D'Addazio, Laboratory of Virology, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Rome, Italy.
	19-22	The 26th Annual Meeting of the Canadian Congress of Neurological Sciences, Halifax (Nova Scotia) Sheraton. Contact Permanent Secretariat, Canadian Congress of Neurological Sciences, 810-906 12th Ave SW, Calgary, Alberta, Canada T2R 1K7; (403) 229-9544.
	20-23	The 66th Annual Meeting of the American Association of Neuropathologists, Omni Innerharbor Hotel, Baltimore, Md. Contact Reid R. Heffner, Jr, MD, Department of Pathology, 204 Farber Hall, State University of New York at Buffalo School of Medicine, Buffalo, NY 14214; (716) 898-3114.
	21-23	"Current Concepts in Child Neurology," Hyatt Islandia Hotel, San Diego, Calif. Contact Continuing Medical Education, Children's Hospital and Health Center, 8001 Frost St, San Diego, CA 92123; (619) 576-1700.
	23-29	Ninth European Congress of Neurosurgery, Moscow, Union of Soviet Socialist Republics. Contact Organizing Committee, Ninth European Congress of Neurosurgery, 5 Fadeev St, Moscow 125047, Union of Soviet Socialist Republics.
	26-28	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," The Snowmass Conference Center, Snowmass Village, Colo. Contact Susan Mitchell, EdD, 2929 Race St, Fort Worth TX 76111; (817) 831-2604.
	27-29	"Clinical Neuro-Oncology Update," Towsley Center, Ann Arbor, Mich. Contact Julie Jacobs, Towsley Center for Continuing Medical Education, Department of Postgraduate Medicine, The University of Michigan Medical School, PO Box 1157, Ann Arbor, MI 48106-9869; (313) 763-1400.
	29-July 3	Fifth International Headache Congress, Washington, DC. Contact the Fifth International Headache Congress, 22 Euclid St, Woodbury, NJ 08096; (609) 845-7220.
July	1-5	Third Meeting of the International Neurotoxicology Association, Parma, Italy. Contact Dr A. Mutti, Organizing Secretary, Laboratory of Industrial Toxicology, University of Parma, Via Gramsci 14, I-43100, Parma, Italy.
	7-10	23rd Annual March of Dimes Clinical Genetics Conference, Vancouver, British Columbia. Contact March of Dimes, 1275 Mamaroneck Ave, White Plains, NY 10605; (914) 428-7100.
	10-13	International Workshop on Huntington's Disease, Cardiff, Wales. Contact Professor P. S. Harper, Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff, CF4 4XN, Wales.
	15-19	14th Annual Contemporary Clinical Neurology Symposium, The Conference Center at Palmetto Dunes Resort, Hilton Head Island, SC. Contact Marsha Bain, Vanderbilt Division of Continuing Medical Education, D-8211 Medical Center North, Nashville, TN 37232-2337; (615) 322-4030.
August	7-9	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," Sheraton Inn and Conference Center, Worcester, Mass. Contact Susan Mitchell, EdD, 2929 Race St, Forth Worth, TX 76111; (817) 831-2604.
	14-18	The Second Dartmouth International Conference on the Corpus Callosum and Epilepsy, Dartmouth-Hitchcock Medical Center, Hanover, NH. Contact Alexander G. Reeves, MD, Section of Neurology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.

Damasio Selected to Receive American Medical Association Award.—An international leader in the field of cognitive neuroscience at the University of Iowa College of Medicine, Iowa City, was selected to receive the American Medical Association's Dr William Beaumont Award for 1990.

Dr Antonio R. Damasio, Maurice Van Allen professor and head of the neurology department, was chosen to receive the award presented annually to a physician, under age 50 years, who has made an outstanding contribution to medical research. This is one of five major honors awarded by the association at its annual convention, June 24 through 28, in Chicago.

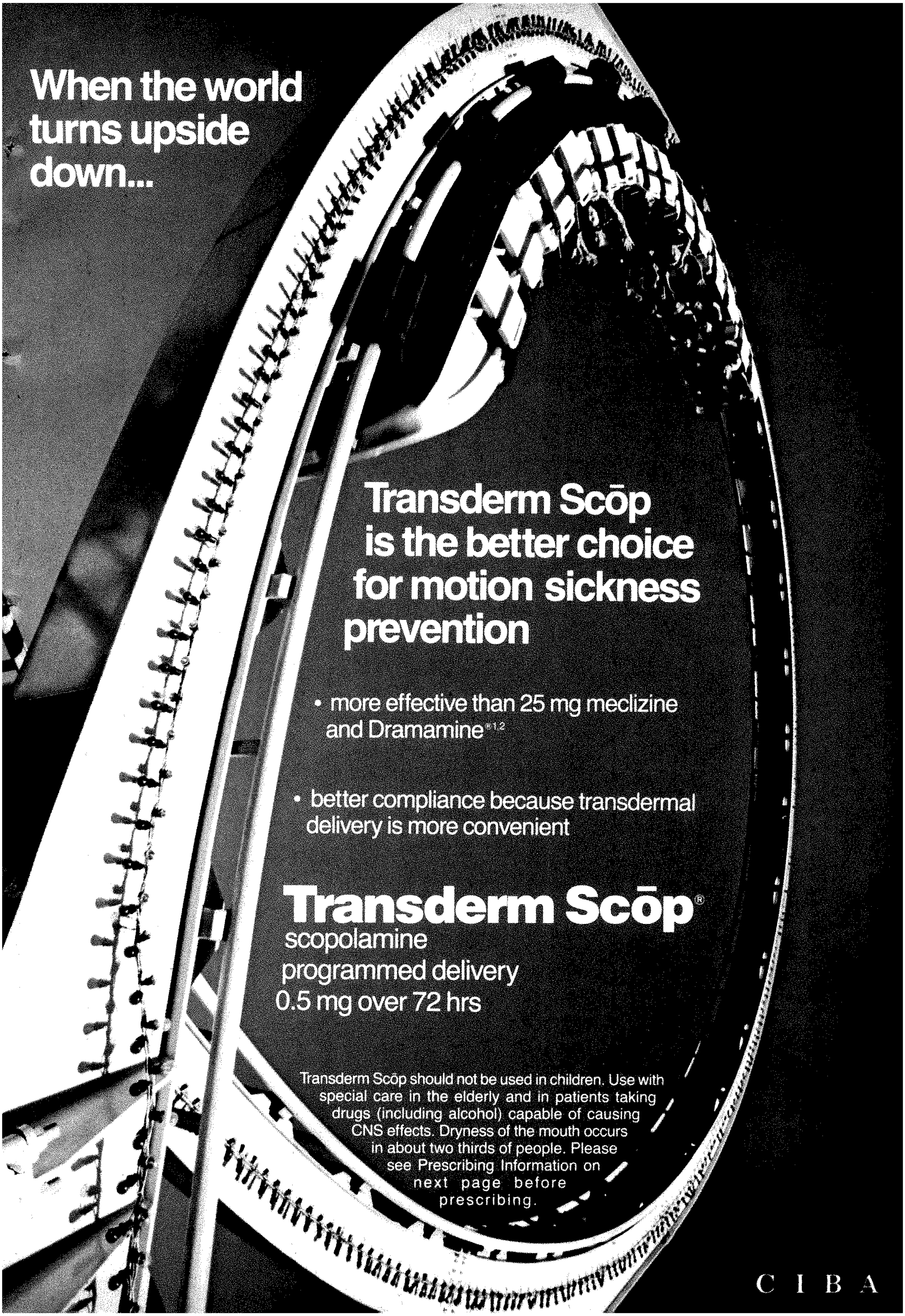
For the past 15 years, "Dr Damasio has made landmark contributions to the understanding of the areas of the brain responsible for mental activities; this award recognizes him as a leader in the field of cognitive neuroscience," says Dr John W. Eckstein, dean of the University of Iowa College of Medicine.

Damasio and his colleagues have identified areas of the human brain that are critical for color perception, reading, and face recognition; shown that the brain assigns different types of knowledge, such as man-made objects, natural kinds, language codes, and social conduct, to entirely different neural systems; and discovered that Alzheimer's disease destroys specific nerve cells in a particular area of the brain, and that the cell loss is accompanied by degeneration of a brain neurotransmitter pathway. These specific changes are a key mechanism behind the memory loss, the hallmark of Alzheimer's disease.

The Dr William Beaumont Award consists of a cash stipend and a plaque that was presented to Dr Damasio during an award ceremony at the association's annual convention.

American Board of Psychiatry and Neurology Inc.—The following individuals were certified in neurology at the examination held in October 1990:

Achenbach-Ng, Jane Marie
Allis, Barbara Ann
Apfel, Stuart Charles
Argoff, Charles Evan
Astruc, Juan
Balish, Marshall Samuel
Bambakidis, Peter
Bazan, Julius Alexander
Beer, Ernesto Fernandez
Benardo, Larry S.
Benjamin, Jeffrey Lewis
Bertram, Edward Hiltner III
Besser, David Lee
Bird, Shawn Joseph
Blady, David
Boltz, Frederick Joseph
Boor, Darwin Russell
Bradshaw, Deborah Young
Brazin, Myron Errol
Burdick, Jeffrey J.
Cantor, Gordon Michael
Chehebar, Victor
Choy-Kwong, Maria
Coats, Michael Edwin
Coin, J. Thaddeus
Colicchio, Alan Robert
Coll, John Bernard
Conwit, Robin Andrea
Corboy, John Richard
D'Angelo, Marc Scott
David, William Samuel
Davis, Thomas Lee
DeCarli, Charles Steven
DeSousa, Garcia Jose
Deputy, Glenn Edward
Dietz, Mark Alan
Doherty, Elizabeth Anne
Dooneief, George Harman
Drubach, Daniel Alejandro
Echiverri, Henry Caoili
Estol, Conrado Jose
Finkelman, Richard Scott
Floeter, Mary Kay
Gelblum, Jeffrey Barton
Gilbert, Mark Richard
Gizzi, Martin S.
Glass, Jonathan David
Goldstein, Steven
Goodsett, Mary Louise
Gordon, Marc Lawrence
Graham, Glenn David
Gray, James Thomas, Jr
Greene, Paul Edward
Greenspan, Beverly Naomi
Grewal, Raji Paul
Grossman, Murray
Grosz, Raul
Grundman, Michael
Guarino, Rosario
Gzesh, Dan Jonathan
Haber, Laurence David
Hammack, Julie Elaine
Harris, Mark I.
Helmers, Sandra L.
Hess, David Charles
Heyman, Rock Alan
Hoffman, Donald Lawrence
Hughes, Donna Rae
Hurtt, Mark Richard
Hyde, Thomas Michael
Hyder, Syed Shiraz
Jaitly, Rakesh
Jindal, Surinder Paul
Johnson, Gary Darrell
Khella, Sami Lewis
Kieburtz, Karl David
Klein, Pavel
Knepper, Laurie Elizabeth
Kolkin, Seth
Kolson, Dennis Larry
Kostyk, Sandra Ksenia
Kramer, Eric Dale
Kranzler, Leon Stephen
Krauss, Gregory Lewis
Kurtzke, Robert Nevin
L'Europa, Gary Anthony
Labutta, Robert Joseph
Langer, Sara Lynn
Laterra, John Joseph
Lazarus, Kenneth Jay
Leifer, Dana
Levey, Allan Ira
Lim, Adoracion Co
Lombardo, Mark Anthony
Lopez-Bresnahan, Maria Victoria
Luciano, Carlos Alberto
MacLean, Gregg Lamont
Madrid, Ricardo Eugenio
Maher, Leo M.
Majumdar, Lisa Ann
Maloon, Alan
Maraganore, Demetrius M.
Marini, Ann Marie
Markind, Samuel Harris
Matthews, Michael Kukuvka, Jr
Mazdzer, Edward James
Mazlin, Steven Eric
McCarthy, Andrew Denis
McCarthy, David Daniel
McDermott, Flordeliza Miranda
Medved, Louis Howard
Memon, Zaitoon Iqbal
Mendelson, Stuart Gene
Milrod, Lewis Martin
Minieka, Michael Mark
Mishra, Bibhuti Bhushan
Moorthy, Gita
Moray, Jonathan Scott
Motiwala, Rajeev S.
Mulpur, Tejanand Gowtham
Nemani, Sajjan Kumar
Oakes, William Thomas, Jr
Otis, James A. D.
Paleologos, Nina A.
Patel, Shreyas Vinubhai
Paul, John Thomas
Perel, Allan Brian
Peterson, Alison Reichard
Picone, Maryann
Pitem, Michael Irwin
Polisetty, Usha S.
Poole, Patrick Evan
Preston, David Channing
Prusinski, Christopher Joseph
Raab, Vicki E.
Raedy, Melany
Rahman, Syed Habeebur
Rapcsak, Steven Z.
Rappaport, Bob Andrew
Reim, Johannes Wolfgang
Reincke, Martha Hanna Elisabeth
Rezak, Michael
Rich, Jaime Marie
Richards, Bruce Alfred
Riser, Emily Sherrill
Riser, John Byron
Ritaccio, Anthony Louis
Roberts, Paul Joseph
Roifer, Deborah R.
Rosen, Steven Alan
Rosenfeld, Myrna Rachel
Rothstein, Jeffrey David
Royal, Walter III
Salazar-Grueso, Edgar Fernando
Samuels, Todd Louis
Schecter, Jay Alan
Scherer, Steven Simon
Schneider, Lori Beth
Scott, Thomas Francis
Seliger, Marlon Stuart
Shapiro, Barbara Ellen
Shatz, Rhonna Sachs
Shtybel, Wayne Wesley
Tick Chong, Peter Siao
Silverman, Stuart Lee
Singleton, Lafayette
Snodgrass, Susan Miguel
Sollenberger, Stanton Edward
Stearns, Michael Quentin
Stolz, Sarah Ellen
Stone, James Leland
Taber, Jesse Eugene
Tang, Cha-Min
Tatum, William Otis IV
Thadani, Vijay Michael
Thorsen, Robert Scott
Tietjen, Gretchen Elizabeth
Usher, Gary David
VanLandingham, Kevan Epes
Vogel, Caryn Miriam
Vogt, Walter A.
Walsh, Christopher
Wassermann, Eric Michael
Weissman, Joseph Daniel
Woodcock, Jonathan Hugh
Worthington, Andrew Keith
Yen, Catherine Eleanor
Young, William Boyd
Zimmerman, Barry Lewis



When the world turns upside down...

Transderm Scōp is the better choice for motion sickness prevention

- more effective than 25 mg meclizine and Dramamine®[1,2]
- better compliance because transdermal delivery is more convenient

Transderm Scōp®
scopolamine
programmed delivery
0.5 mg over 72 hrs

Transderm Scōp should not be used in children. Use with special care in the elderly and in patients taking drugs (including alcohol) capable of causing CNS effects. Dryness of the mouth occurs in about two thirds of people. Please see Prescribing Information on next page before prescribing.

CIBA

Transderm Scōp®

scopolamine
(formerly Transderm-V)

Transdermal Therapeutic System

Programmed delivery *in vivo* of 0.5 mg of scopolamine over 3 days

BRIEF SUMMARY (FOR FULL PRESCRIBING INFORMATION, SEE PACKAGE INSERT)

INDICATIONS AND USAGE

Transderm Scōp is indicated for prevention of nausea and vomiting associated with motion sickness in adults. The disc should be applied only to skin in the postauricular area.

Clinical Results: Transderm Scōp provides antiemetic protection within several hours following application of the disc behind the ear. In 195 adult subjects of different racial origins who participated in clinical efficacy studies at sea or in a controlled motion environment, there was a 75% reduction in the incidence of motion-induced nausea and vomiting. Transderm Scōp provided significantly greater protection than that obtained with oral dimenhydrinate.

CONTRAINDICATIONS

Transderm Scōp should not be used in patients with known hypersensitivity to scopolamine or any of the components of the adhesive matrix making up the therapeutic system, or in patients with glaucoma.

WARNINGS

Transderm Scōp should not be used in children and should be used with special caution in the elderly. See **PRECAUTIONS.**

Since drowsiness, disorientation, and confusion may occur with the use of scopolamine, patients should be warned of the possibility and cautioned against engaging in activities that require mental alertness, such as driving a motor vehicle or operating dangerous machinery.

Potentially alarming idiosyncratic reactions may occur with ordinary therapeutic doses of scopolamine.

PRECAUTIONS

General

Scopolamine should be used with caution in patients with pyloric obstruction, or urinary bladder neck obstruction. Caution should be exercised when administering an antiemetic or antimuscarinic drug to patients suspected of having intestinal obstruction.

Transderm Scōp should be used with special caution in the elderly or in individuals with impaired metabolic, liver, or kidney functions, because of the increased likelihood of CNS effects.

Information for Patients

Since scopolamine can cause temporary dilation of the pupils and blurred vision if it comes in contact with the eyes, patients should be strongly advised to wash their hands thoroughly with soap and water immediately after handling the disc.

Patients should be advised to remove the disc immediately and contact a physician in the unlikely event that they experience symptoms of acute narrow-angle glaucoma (pain in and reddening of the eyes accompanied by dilated pupils).

Patients should be warned against driving a motor vehicle or operating dangerous machinery. A patient brochure is available.

Drug Interactions

Scopolamine should be used with care in patients taking drugs, including alcohol, capable of causing CNS effects. Special attention should be given to drugs having anticholinergic properties, e.g., belladonna alkaloids, antihistamines (including meclizine), and antidepressants.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate carcinogenic potential. Fertility studies were performed in female rats and revealed no evidence of impaired fertility or harm to the fetus due to scopolamine hydrobromide administered by daily subcutaneous injection. In the highest-dose group (plasma level approximately 500 times the level achieved in humans using a transdermal system), reduced maternal body weights were observed.

Pregnancy Category C

Teratogenic studies were performed in pregnant rats and rabbits with scopolamine hydrobromide administered by daily intravenous injection. No adverse effects were recorded in the rats. In the rabbits, the highest dose (plasma level approximately 100 times the level achieved in humans using a transdermal system) of drug administered had a marginal embryotoxic effect. Transderm Scōp should be used during pregnancy only if the anticipated benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether scopolamine is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Transderm Scōp is administered to a nursing woman.

Pediatric Use

Children are particularly susceptible to the side effects of belladonna alkaloids. Transderm Scōp should not be used in children because it is not known whether this system will release an amount of scopolamine that could produce serious adverse effects in children.

ADVERSE REACTIONS

The most frequent adverse reaction to Transderm Scōp is dryness of the mouth. This occurs in about two thirds of the people. A less frequent adverse reaction is drowsiness, which occurs in less than one sixth of the people. Transient impairment of eye accommodation, including blurred vision and dilation of the pupils, is also observed.

The following adverse reactions have also been reported on infrequent occasions during the use of Transderm Scōp: disorientation; memory disturbances; dizziness; restlessness; hallucinations; confusion; difficulty urinating; rashes and erythema; acute narrow-angle glaucoma; and dry, itchy, or red eyes.

Drug Withdrawal: Symptoms including dizziness, nausea, vomiting, headache and disturbances of equilibrium have been reported in a few patients following discontinuation of the use of the Transderm Scōp system. These symptoms have occurred most often in patients who have used the systems for more than three days.

OVERDOSAGE

Overdosage with scopolamine may cause disorientation, memory disturbances, dizziness, restlessness, hallucinations, or confusion. Should these symptoms occur, the Transderm Scōp disc should be immediately removed. Appropriate parasympathomimetic therapy should be initiated if these symptoms are severe.

DOSAGE AND ADMINISTRATION

Initiation of Therapy: One Transderm Scōp disc (programmed to deliver 0.5 mg of scopolamine over 3 days) should be applied to the hairless area behind one ear at least 4 hours before the antiemetic effect is required. Only one disc should be worn at any time.

Handling: *After the disc is applied on dry skin behind the ear, the hands should be washed thoroughly with soap and water and dried. Upon removal of the disc, it should be discarded, and the hands and application site washed thoroughly with soap and water and dried, to prevent any traces of scopolamine from coming into direct contact with the eyes. (A patient brochure is available.)*

Continuation of Therapy: Should the disc become displaced, it should be discarded, and a fresh one placed on the hairless area behind the other ear. If therapy is required for longer than 3 days, the first disc should be discarded, and a fresh one placed on the hairless area behind the other ear.

The system should be stored between 59°-86°F (15°-30°C).

CAUTION

Federal law prohibits dispensing without prescription.

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CIBA Consumer Pharmaceuticals
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Summit, NJ 07901

C88-5 (Rev. 2/88)

C I B A

References:

1. Dahl E: *Clin Pharmacol Ther* 1984;36:116-120. A study of mild motion sickness in a laboratory setting in which Transderm Scōp® demonstrated a significantly greater reduction in the incidence of nausea and vomiting than 25 mg meclizine ($P = 0.01$) and placebo ($P = 0.003$).
2. Price N et al: *Clin Ther* 1979;2:258-262. Studies at sea that demonstrated a 75% mean reduction in the incidence of nausea and vomiting associated with motion sickness with Transderm Scōp, compared to 50% with Dramamine® ($P > 0.05$).

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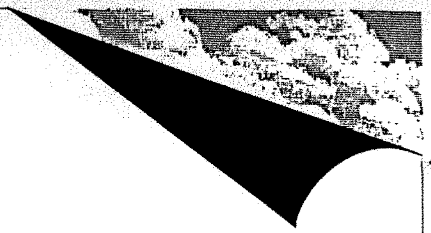

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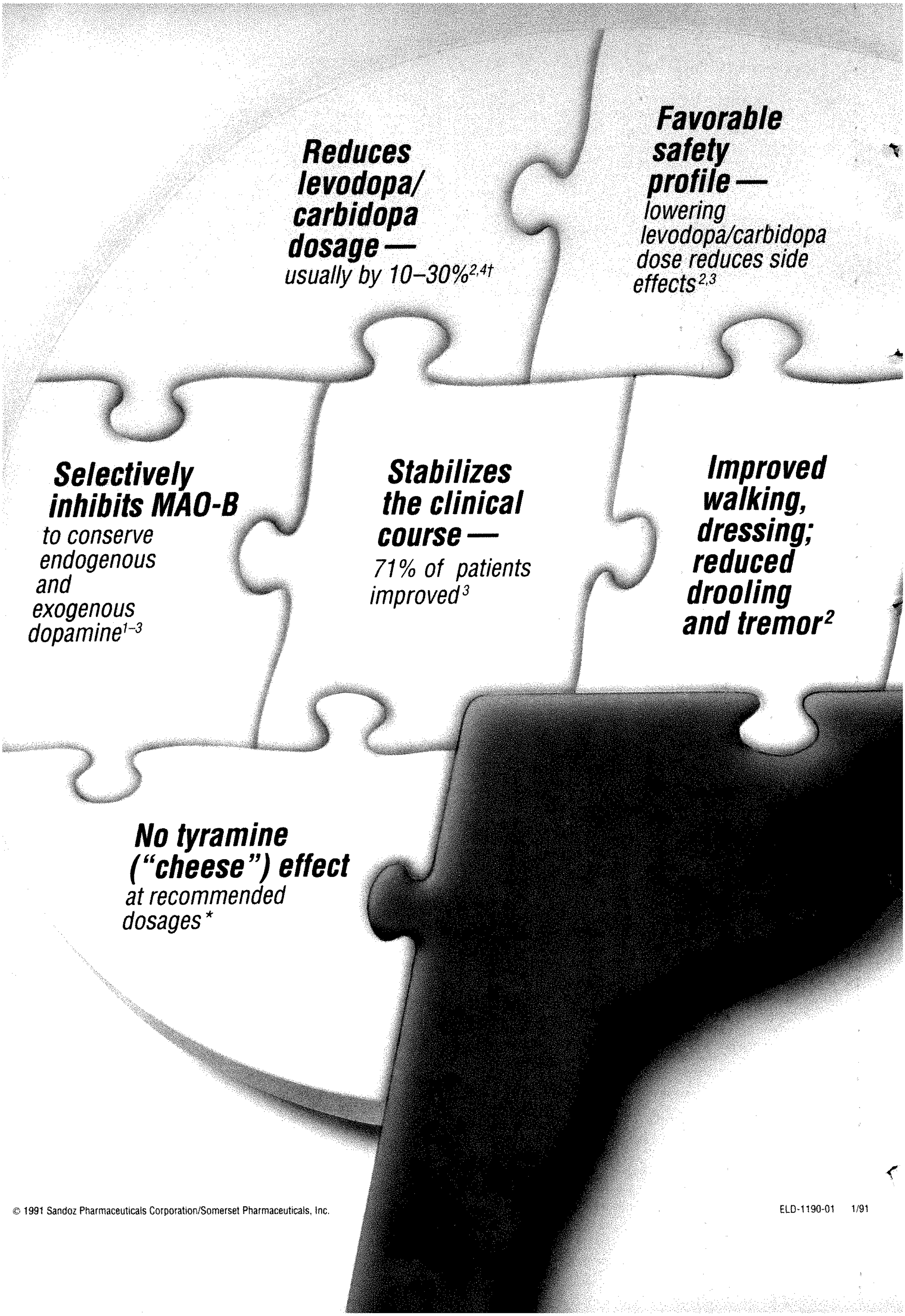

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Favorable safety profile — *lowering levodopa/carbidopa dose reduces side effects[2,3]*

Selectively inhibits MAO-B *to conserve endogenous and exogenous dopamine[1–3]*

Stabilizes the clinical course — *71% of patients improved[3]*

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No tyramine ("cheese") effect *at recommended dosages**

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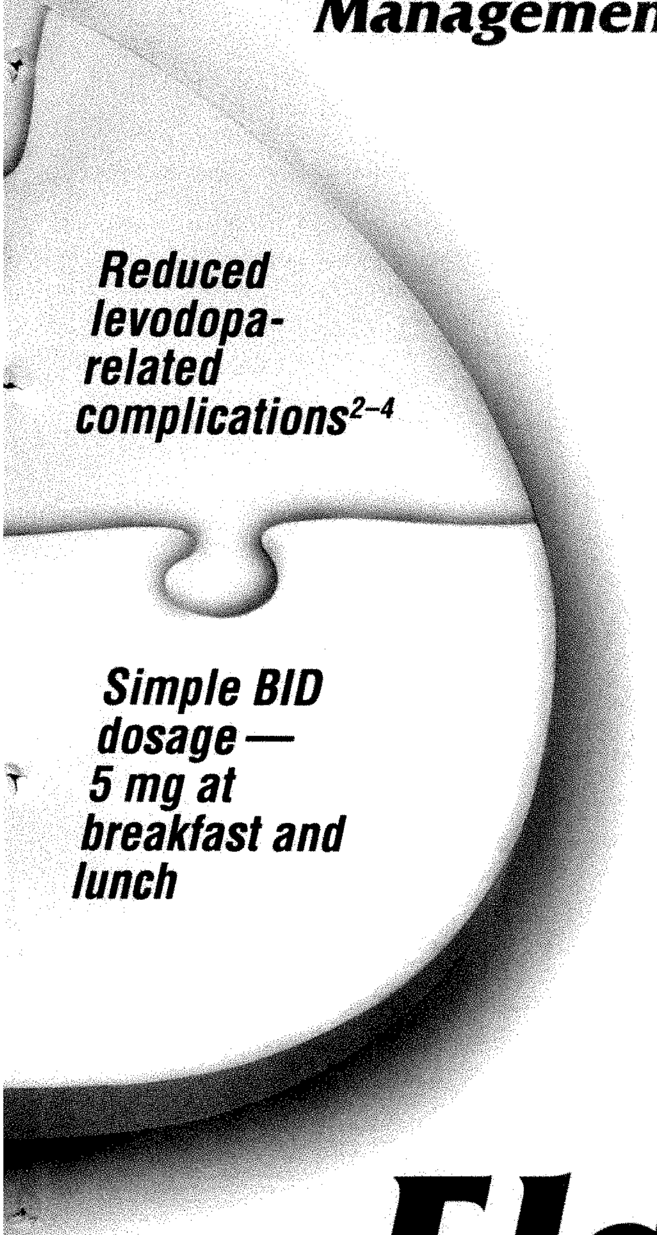
Management of Parkinson's disease...
still a puzzle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†Further reduction of levodopa/carbidopa may be possible during continued selegiline therapy.

See next page for brief summary of prescribing information.

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

BRIEF SUMMARY

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

INDICATIONS AND USAGE:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated in patients with a known hypersensitivity to this drug.

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommenced daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Because of reports of fatal interactions, MAOIs are ordinarily contraindicated for use with meperidine (DEMEROL & other tradenames). This warning is often extended to other opioids. Because the mechanism of interaction between MAOIs and meperidine is unknown, it seems prudent, in general, to avoid this combination.

Definitive clinical data on the concomitant use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) and fluoxetine hydrochloride (PROZAC) is not available. Death has been reported to occur following the initiation of therapy with nonselective MAOI's (NARDIL, PARNATE) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with ELDEPRYL® (SELEGILINE HYDROCHLORIDE), however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately 5 half-lives) should elapse beweeen discontinuation of fluoxetine and initiation of MAOI therapy. Based on experience with the combined use of MAOI's and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with fluoxetine.

PRECAUTIONS:

General: Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients: Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests: No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL® (SELEGILINE HYDROCHLORIDE). Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions: No interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (See WARNINGS and PRECAUTIONS.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: *Pregnancy Category C.* Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use: The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction: The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with ELDEPRYL® (SELEGILINE HYDROCHLORIDE) obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blephorospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM: Dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE: Slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES: Increased sweating, diaphoresis, facial hair, hair loss, hemotoma, rash, photosensitivity.

MISCELLANEOUS: Asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE).

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N = 49	placebo N = 50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

OVERDOSAGE:

Selegiline: No specific information is available about clinically significant overdoses with ELDEPRYL® (SELEGILINE HYDROCHLORIDE). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors (e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)).

Overdose with Non-Selective MAO Inhibition: NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

(AUGUST, 1990 011-25-P-103)

References:

1. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science.* 1989;245:519–522.
2. Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clin Neuropharmacol.* 1988;11(1):45–55.
3. Lieberman AN, Gopinathan G, Neophytides A, et al. Deprenyl versus placebo in Parkinson's disease: A double-blind study. *NY State J Med.* 1987;87:646–649.
4. Presthus J, Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. *Acta Neurol Scand.* 1983;95(suppl):127–133.

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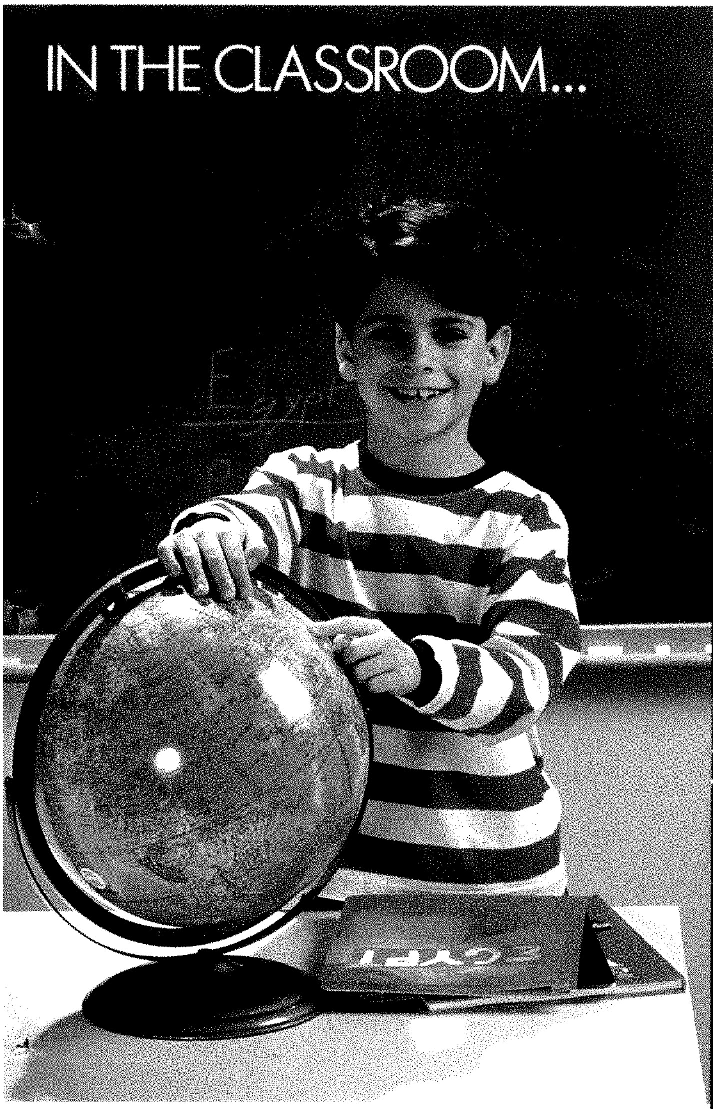
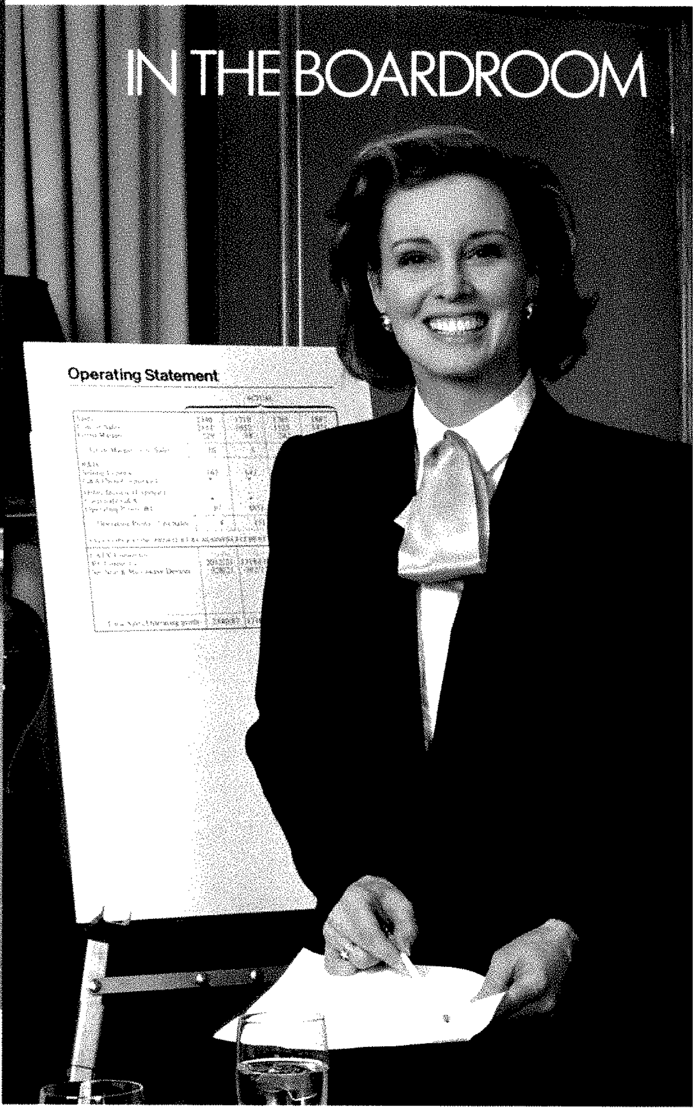
Seizures controlled, thoughts clear, smiles bright





Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

CIBA—GEIGY

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Tegretol®

200-mg scored tablets
100-mg chewable tablets

carbamazepine USP

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

318-4421-A

References
1. Smith DB, Mattson RH, Cramer JA, et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58.
2. Mattson RH, Cramer JA, Collins JF, et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151.
3. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;29:794-804.

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink   Tablets of 200 mg—pink

WARNING
APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

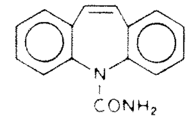
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

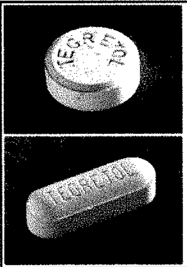
It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System. Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin. Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary.

Cardiovascular System. Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver. Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System. Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System. Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System. Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System. Aching joints and muscles, and leg cramps.

Metabolism. Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration. Irregular breathing, respiratory depression.

Cardiovascular System. Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles. Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract. Nausea, vomiting.

Kidneys and Bladder. Anuria or oliguria, urinary retention.

Laboratory Findings. Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning. When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug. Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption. Activated charcoal, laxatives.

Measures to Accelerate Elimination. Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression. Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock. Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions. Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities. If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.
Protect from moisture.
Dispense in tight container (USP).
Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles.

Printed in U.S.A.   C90-34 (Rev. 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

Books

Neonatal Seizures, edited by Claude G. Wasterlain and Paul Vert, 336 pp, with illus, $98, New York, NY, Raven Press, 1990.

The literature of the epilepsies has burgeoned in the past decade. This is particularly true of pediatric epileptology where basic mechanisms, including molecular biology and genetics; the identification of individual syndromes; and the identification of epileptogenic mechanisms at the neuronal level, the synaptic level, and the higher levels of systems involved in the propagation of the epileptic discharge, have been elucidated.

This book fills a void. Among the identification and classification of epileptic seizures and the epilepsies, knowledge about neonatal seizures has lagged. The lag has been contributed by the difficulty in identifying neonatal seizures, which are frequently subtle and less stereotyped than in the older child, frequently occur in the background of a severe brain disturbance, and depend in their pathophysiology on respiratory and blood flow changes resulting in energy failure in a system with its own fragile autoregulatory mechanisms.

This volume is divided into several sections. These include clinical descriptions of seizures, syndromes, and electroencephalographic changes that bring the patient to the notice of the physician. Basic differences already occur according to the anatomic level of nervous system derangement. The mechanisms of brain damage are discussed at the level of neuronal events, where energy metabolism, selective neuronal vulnerability, and pathologic changes as the result of seizures and status epilepticus are discussed. The metabolism of the immature and neonatal nervous system, the nuances of substrate utilization and blood flow autoregulation, and the use of positron emission tomography and nuclear magnetic resonance imaging in the intact brain are the subject of the next section. A discussion of synaptic events and neurotransmitter pharmacology, including excitatory and inhibitory transmitter mechanisms and the concept of excitotoxins and their consequences, follow. Local circuit changes in specific brain regions, the development of mossy fiber sprouting, and the resulting synaptogenesis and neuronal plasticity involving the molecular layer of the dentate gyrus in experimental epilepsy, are of great current interest and are germane to the evolving rationalization of the therapy of epileptic seizures. The subject of therapy completes the book.

Between the idea and the reality of publication falls the shadow of 3 years in production; yet the volume remains remarkably fresh and current. This book is not just another conference proceeding but represents a major step in illuminating both brain development and the pathophysiology of epilepsy. It is highly recommended to all who strive to better apply the results of neuroscience research to understanding the compromised developing nervous system and translating this understanding to improving rational therapies.

Fritz E. Dreifuss, MB, FRCP, FRACP
Charlottesville, Va

Amyotrophic Lateral Sclerosis. Concepts in Pathogenesis and Etiology, edited by Arthur J. Hudson, 378 pp, $75, Toronto, Ontario, University of Toronto Press, 1990.

This book is a collection of 15 papers presented in 1987. Contributors include the editor, Dr Arthur Hudson, who is the founder of the Amyotrophic Lateral Sclerosis (ALS) Society of Canada, and Drs Antel, Calne, Dalakas, Eisen, Gajdusek, Hirano, Kurland, and others who have been important, long-time students of ALS and other neurodegenerative disorders. The interest of the presentations ranges broadly. This is a sampling of observations put forth in some of the reports: "Use of cultured human fetal spinal cord neurons currently represents the most promising model system in which to explore the cause of ALS." "Sera from a proportion of patients with ALS and other denervating diseases produce a . . . decrease [sic] of motoneuron death during embryonic development." "Classic ALS . . . apparently results in impaired metabolism of gangliosides, which leads to rapid death of motor neurons." "Understanding of the molecular basis of the retrovirus-induced motor neuron disease in mice . . . we hope will help to [prevent and treat human neurodegenerative diseases]." "The . . . data indicate a failure as yet to detect unique antibodies interacting with motor neurons in ALS." Motor neuron diseases "clinically indistinguishable [from classic sporadic ALS] include familial ALS, Western-Pacific ALS, post-encephalitic ALS, and a presumably infective form of disease [following a cat bite]."

A special feature of this volume is the considerable attention paid to the Western-Pacific form of ALS and its changed incidence as well as its controversial link to dietary habits.

The book is well presented, with care unusual for the product of a symposium. Some of the discussions, such as that concerning the pathologic basis of the disease, are very useful resources that should outlive the usual lifespan of this type of collection. To read this book is to gain some assurance that those of us who are practicing last-century medicine in caring for our patients with ALS have reason to hope that the treatment of the disease will move into the modern era. The hopefulness that this creates in practitioners cannot help but reach our patients and their families. It is clear that the investigators who compiled this book have that ultimate objective in mind.

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Imaging of the Nervous System, by Paul Butler, 271 pp, with illus, $198, New York, NY, Springer-Verlag Inc, 1990.

This book presents a well-written overview of the imaging modalities of the central nervous system. Computed tomographic scanning, magnetic resonance imaging, angiography, myelography, plain-film radiography, duplex sonography, and isotope imaging are discussed; the primary emphasis is on computed tomographic and magnetic resonance imaging. The first chapter discusses cerebrovascular disease with an excellent review of the pertinent findings of cerebral infarction on computed tomography. The pattern of attenuation and enhancement, hemorrhage, mass effect, vascular territory, age of the infarct, and the differential diagnosis are covered in depth. The difficult subject of discussing the varied causes of cerebrovascular disease is concisely handled. Other well-written chapters discuss intracranial tumors, hydrocephalus and degenerative diseases, trauma, infections, pediatric neuroimaging, spine imaging, orbit imaging, temporal bone imaging, the muscular and peripheral nervous system, and isotope imaging.

The text is well organized and is concisely written. The information is practical, current, and well referenced. The printing is legible, the legends are informative, and the illustrations are of high quality.

The need for a concise up-to-date summary of central nervous system imaging is well fulfilled by this book. Although this book is useful to all radiologists, neurologists, and neurosurgeons, it is especially well suited for residents in training. In addition, this text would serve as an excellent reference in medical libraries for medical students and practicing physicians and surgeons.

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Essentials of Child Neurology, by Suresh Kotagal, 192 pp, $42, St Louis, Mo, Ishiyaku EuroAmerica Inc, 1990.

Essentials of Child Neurology is another in the recent spate of minitextbooks on pediatric neurology. As stated by the author in the preface, this book attempts to provide an intermediate-length summary of the discipline.

The book's chapters vary from topic-oriented to symptom- or sign-oriented and provide succinctly written summaries of major problems in clinical pediatric neurology. The book begins with a brief introduction to the neurologic history and the examination of the infant and young child, emphasizing the developmental factors that influence neurologic findings. Chapter 1's section, "Commonly observed Neurological Manifestations," represents a useful glossary of neurologic terms. Inclusion of concise definitions of neurologic jargon is a laudable feature throughout the text.

Subsequent chapters cover numerous topics in pediatric neurology, including infections of the central nervous system, seizure disorders, neurocutaneous syndromes, neuromuscular conditions, and neurodegenerative disorders, to name but a few. Most information is accurately presented, and the book contains sufficient detail regarding contemporary therapeutic modalities for many disorders. The well-written chapter describing sleep disorders as well as the chapters on seizure disorders and neurologic emergencies provides practical information relevant to residents and practitioners.

The book does a commendable job of incorporating information regarding developmental disabilities and school failure, topics that are frequently considered on the fringe of traditional pediatric neurology. By contrast, tumors of the nervous system and the neurologic complications of systemic illnesses receive only cursory mention. Readers would be well served by additional material regarding neoplasms of the central nervous system and the expanding role for chemotherapy in the treatment of such tumors.

Although the chapters per se are generally well organized and include an introductory outline, the sequencing of chapters could be improved. The chapter describing "Common Neurodiagnostic Procedures" would more logically follow the chapter on "Clinical Assessment," and the nicely written chapter on "Neonatal Neurology" could be juxtaposed with the section describing the "Development of the Nervous System and its Aberrations." The text could also indicate more clearly the relative prevalence of disorders that constitute a specific differential diagnosis.

The book contains several tables and algorithms that appropriately supplement material in the text. Certain tables, particularly those summarizing central nervous system storage disorders and hereditary neuropathies, incorporate abundant, valuable clinical details. In general, the algorithms provide useful information regarding the formulation of a differential diagnosis. Each chapter concludes with a modest number of references or suggestions for further reading.

A few publishing glitches detract from the overall quality of Dr Kotagal's effort. The type seemed a bit fuzzy in places, and some illustrations lacked clarity or were off-center. The book sent for review was missing pages 25 through 32, an error hopefully limited only to this copy. Occasional typographical errors, eg gentamycin and ethosuxamide, were also detected. Despite these flaws, *Essentials of Child Neurology* achieves its goal and constitutes a readable, introductory-level text suitable for students, residents-in-training, and many practitioners.

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Delirium: Acute Confusional States, by Z. J. Lipowski, 490 pp, $69.50, New York, NY, Oxford University Press, 1990.

Delirium is an erudite, comprehensive treatment of a difficult yet important subject. Z. J. Lipowski deserves credit for bringing together many areas of widely discrepant opinions, descriptions, and explanations for the complex phenomena that can be observed in acute confusional states or delirium. As there is a great deal of variability in symptomatology, delirium is a difficult problem to study. The patients are usually quite ill, uncooperative, and difficult to examine, and the phenomena of delirium is transient. All of this explains the scarcity of systematized research and the abundance of anecdotal descriptions. Delirium is one of the few abnormal mental phenomena that has been experienced by almost everyone. Most of us have gone through a febrile state in childhood with vivid, dreamlike hallucinations and remember the horrifying experience.

The definition of delirium to encompass all forms of confusional states will not sit well with everybody. Most people would define the term *delirium* to be an acute confusional state with restless and excited behavior. This argument over terminology is reflected in the lengthy chapters on the history of delirium and the definition of terms. The definition of delirium in the *Diagnostic and Statistical Manual of Mental Disorders*, third edition (*DSM III*), is overinclusive and nonspecific at the same time and is not very helpful in defining this common and characteristic clinical phenomena. It would not be the first time that attempts by a few experts from "above" failed to match the general usage, and it would not be the first time a pedantic definition in the *DSM III* turned out to be inadequate shortly after it was written. There are plenty of reasons to object to lumping patients with reduced alertness and decreased psychomotor activity into the category of delirium, which is distinguished by increased verbal, psychomotor, and autonomic activity. The author himself lists a number of these. The usefulness of this distinction should be evident to most of those who have been called on to diagnose the cause of confusion in a febrile child, an alcoholic, or in one who overdosed on drugs. I suspect that this distinction will continue to be used and remain important, despite efforts by the author and others to consider it a manifestation of delirium.

In the description of symptoms, one cannot help but think that some of these represent different disease processes at one time or another. For example: "As the severity of delirium grows, the patient becomes increasingly distractible and either drowsy and lethargic or hyperalert and agitated . . . . Concurrently, thinking becomes increasingly labored and slow or rapid, but incoherent." The overinclusive descriptions are not very useful, such as "the speed, frequency, and loudness of vocalization are often increased or decreased in delirium. Speech is absent on occasion and the patient is mute. At the other extreme, a ceaseless flow of speech, often repetition of the same words or phrases, tends to be part of a general overactivity." Surely such widely discrepant phenomena represent different origins and different mechanisms. In a comprehensive book such as this, one would expect more emphasis on specificity and analysis rather than generalization. The author seems to have left out the interesting phenomena of reduplication and the Capgras syndrome. I could not find any listing for these in the index.

The descriptive chapter on hallucinations and their psychopathology is well done. Recent knowledge concerning serotonin metabolism in dreams and drug-induced hallucinations and some of the studies concerning the primary visual nature of hallucinations are interesting. On the other hand, disorders of memory are reviewed somewhat superficially. The chapter on predisposing and facilitating factors and etiology is well organized. Particularly extensive is the review of sleep-deprivation studies. The treatment of delirium is well referenced and is one of the most useful chapters in the first part of the book.

The second part of *Delirium* deals with the more specific causes of this disorder, the most important one being drug intoxication. I think this is one aspect of clinical medicine that is relevant to almost all disciplines. The important concept of confusional states as a cognitive, attentional disturbance, induced by cholinergic blockade, is expanded in the chapter on anticholinergic toxicity. Cholinergic deficiency may be a common denominator in many other metabolic toxic encephalopathies that produce a reduced rate of acetylcholine synthesis.

The section on toxic substances is brief and will require the reader to use the references extensively for more specific information. Alcohol is given the substantive treatment it deserves. The chapter on metabolic encephalopathies and infections is fairly current and even includes the acquired immunodeficiency syndrome. However, it does not deal specifically with herpes simplex encephalitis, which must be one of the most specific causes of treatable confusional states. This chapter only mentions the periodic complexes in relation to herpes. One would like to have seen the differential diagnosis and a description of neuroimaging and treatment.

This is a useful book for any physician's library, and I expect that in the future I will make frequent use of it myself. It is particularly recommended for neurologists, internists, psychiatrists, and specialists in intensive care medicine.

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Lesion Analysis in Neuropsychology, by Hanna Damasio and Antonio R. Damasio, with illus, $42.95, New York, NY, Oxford University Press, 1989.

The lesion method in studying brain-behavior relationships has had a stormy history. The excellent book by Hanna and Antonio R. Damasio should greatly strengthen the value of this method. As I looked over the excellent brain images with their accompanying neuroanatomical templates, one could wistfully hope that Broca could see what he started.

The Damasios, cognizant of the classic contributions and knowledgeable from their own extensive research, do not make the errors that have plagued neuropsychology and have eroded the value of the lesion method. They remind us again of some fundamental concepts and give illustrative case histories to buttress these concepts. First, they emphasize, as did Hughlings Jackson, that the loss of a function with a specific lesion does not mean the construct for that function resided there. Second, they note that only with careful testing and breaking down a response to its component parts can we understand what role the lesion played in its disruption—a lesson taught us by Luria. Third, they dispel the notion that associating a syndrome with a lesion does not mean that there is necessarily some common feature to all elements of the syndrome. This was a lesson learned from their great teacher, Arthur Benton, who critically analyzed the Gerstmann syndrome. Fourth, they avoid the mistake of pre-World War II neurologists who made inferences from well-described single anatomicoclinical case reports and post-World War II psychologists who described extensive series of patients without good anatomic descriptions. They use multiple single case reports combining the best of the well-described single case and the value of a series of patients. Fifth, they do not make the mistake of assuming all of us have similar wiring diagrams unaffected by experiences, language formation, and other subtle factors, so that behavior may vary from patient to patient with similar lesions.

The methods portion illustrates the painstaking work that is necessary to produce their discrete lesion localization. This, combined with their testing methods, have contributed greatly to our understanding of many different clinical entities, such as prosopagnosia, aphasias, memory problems, and others.

The theoretical portion introduces some novel concepts. The authors reject the notion that bilateral lesions of the multimodal sensory cortices destroy perceptual experience. They introduce the concept of "convergence zones." Essentially, they build their theory on my view of the justification of a neuroanatomy course, "Everything in the brain is connected to everything else—unfortunately, some of the connections have names." They suggest on the basis of their studies that multiple regions of the brain cooperate in a reciprocating fashion, both anterograde and retrograde, to create an internal representation of the stimulus in a convergence zone. Not only does their work buttress this notion, but recent electrophysiological findings of widespread synchronization of neural regions to a stimulus suggest wide and diverse participation in sensory interpretation.

The last part of the book is an elegant description, along with examples, of the methods of localization largely developed by Hanna Damasio. The advantages and pitfalls of her method are fully discussed.

The contribution of these two investigators to the field of brain-behavior linkages are immense. They have again demonstrated that the lesion method is the major means of understanding brain function.

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Letters to the Editor

Letters to the editor should be submitted as an original and two duplicates. They should be typewritten double-spaced on plain bond paper; they will be subject to editing. If they are prepared on a word processor, do not justify the right margin. A copyright transmittal letter signed by all authors must accompany this (see "Instructions for Authors").

Magnetic Resonance Imaging Hyperintensities in Alzheimer's Disease

To the Editor.—This letter is a commentary on Leys and coworkers' article in the May 1990 issue of the ARCHIVES.[1] We commend Leys and coworkers on their effort to determine the significance of white matter and periventricular changes in patients with Alzheimer's disease. The pathological significance of these changes are particularly difficult to assess since, as Leys and coworkers indicate, they are found in many neurologically and psychiatrically normal controls. However, we feel that several methodological issues may make it difficult to generalize the findings in this study. First, the authors excluded 11 of 31 subjects due to poor quality in magnetic resonance imaging scans. They were not clear why more than one third of the patients with Alzheimer's disease had technical difficulties in imaging. We agree with the authors' concern that exclusion on the basis of an inability to cooperate with the magnetic resonance imaging scan may have lead to a skewing of the sample toward healthier patients with Alzheimer's disease. The relatively small magnet size and large interslice gap of 6 mm would also have made their detection of white matter lesions less sensitive.

Second, the authors are not clear why they rate an interobserver agreement on all original 42 subjects since they described technical problems in the scans of 11 subjects. These poor-quality scans would probably have been more difficult to read and have lowered the interobserver agreement. Poor interobserver agreement clearly is a concern when judging the accuracy of the data.

Third, the authors' conclusion that there was no correlation noted between age or Mini-Mental Status Examination and periventricular hyperintensities may be due to the relatively small sample size and narrow age range of their subjects. A number of studies have shown that white matter changes occur with increased frequency in "normal" aging (eg, Drayer et al[2]), and data from our group using 39 normal control subjects confirm this finding with subcortical hyperintensities.[3] The fact that there was no age correlation may indicate that the age range of their subjects was too narrow.

Fourth, the authors failed to mention whether the subjects had a history of mood disorders. This would have been interesting since white matter disease has been found in increased frequency in patients with late-onset depression[4] and late-onset mania.[5]

Finally, the authors mix early- and late-onset patients with Alzheimer's disease, although there is evidence that these may represent two distinct patient groups.[6]

The use of neuroimaging in the workup of the demented patient continues to be a necessary and important tool. Continued study of the significance of white matter and periventricular lesions is essential in this process.

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1. Leys D, Soetaert G, Petit H. Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Arch Neurol.* 1990;47:524-527.

2. Drayer BP. Imaging of the aging brain, I: normal findings. *Radiology.* 1988;166:785-796.

3. Doraiswamy PM, Figiel GS, Husain MM, et al. Subcortical changes in normal aging. *Biol Psychiatry.* 1990;27(suppl 9A):124.

4. Krishnan KRR, Goli V, Ellinwood EH, et al. Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry.* 1988;23:519.

5. McDonald WM, Krishnan KR, Doraiswamy PM, Blazer DG. The occurrence of subcortical hyperintensities in elderly subjects with mania. *Biol Psychiatry.* 1990;27(suppl)9A-162A.

6. Heston LL, Mastri AR, Anderson VE, et al. Dementia of the Alzheimer type: clinical genetics, natural history, and associated conditions. *Arch Gen Psychiatry.* 1981;38:1085-1090.

To the Editor.—In an imaging study of Alzheimer's disease and normal aging, Leys et al,[1] using our rating scale,[2] found no difference in magnetic resonance imaging white matter hyperintensities between the two groups, and only *a trend toward increased periventricular hyperintensity in patients with Alzheimer's disease.* This is in contrast to our initial observation of a hyperintense "halo" in six of 12 cases of Alzheimer's disease.[2] We would like to emphasize, however, that a part of us (F.F., R.S., H.O.) could not replicate this finding in a subsequent study performed under similar conditions. There still remains a trend toward more signal abnormalities in Alzheimer's disease, however. The Table summarizes the current data from subjects without cerebrovascular risk factors in this ongoing project.[3]

A disproportionately higher number of patients with more marked ventricular enlargement in our first study appears to be the likeliest explanation for these discordant findings, since we observed a close correlation between ventricular size and the periventricular hyperintensity area by planimetric analysis (unpublished results). Similar findings to that of Leys et al were also reported by another group pursuing a similar study design.[4]

We are in agreement with Leys et al in terms of imaging findings, but would like to challenge their comments on the usefulness of our scoring scheme:

1. It appears inappropriate to include scans that are technically inadequate for data analysis in a calculation of interobserver agreement. Movement artifacts will strongly obscure border zones such as the periventricular area, and interpretation of small

Prevalence of Magnetic Resonance Imaging Hyperintensities in Study Population Without Cerebrovascular Risk Factors

	Alzheimer's Disease	Control Subjects
Number	16	13
Mean age, y	66 ± 7	64 ± 8
White matter hyperintensities		
None	5	7
Punctate	8	5
Early confluent	3	1
Periventricular hyperintensity		
None	2	6
Caps and/or "lining"	12	7
"Halo"	2	0

punctate foci of increased signal will become quite arbitrary.

2. An uneven level of magnetic resonance imaging interpretation skills among observers with a different background may negatively affect interobserver agreement as well. Kozachuk et al[4] achieved a considerably better interrater reliability with our scoring scheme, reporting a κ coefficient of 0.80 for periventricular hyperintensity and of 0.64 for white matter hyperintensities when scans were interpreted by neurologists only.

3. A simple scoring scheme such as ours will be more likely to yield good interobserver agreement than a complex one. In addition, although Leys et al imply that the more elaborate leukoaraiosis-computed tomographic rating system[5] might be more sensitive to intergroup differences, they present no data to support this.

In conclusion, we think that Leys and coworkers' observation of a minor role of white matter hyperintensities and periventricular hyperintensities in patients with Alzheimer's disease without cerebrovascular risk factors represents a true finding but does not reflect inadequacy of the scoring scheme.

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1. Leys D, Soetaert G., Petit H, Fauquette A, Pruvo JP, Steinling M. Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Arch Neurol.* 1990;47:524-527.

2. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJNR.* 1987;8:421-426.

3. Offenbacher H, Schmidt R, Fazekas F, Payer F, Lechner H. MRI validation of the clinical diagnosis of vascular vs senile dementia of the Alzheimer type. *J Neurol.* 1990;237:147. Abstract.

4. Kozachuk W, DeCarli C, Horwitz B, Schapiro MB, Rapoport SI. White matter changes in dementia of the Alzheimer type (DAT) and healthy controls without cerebrovascular risk factors. *Neurology.* 1990;40(suppl 1):175. Abstract.

5. Rezek DL, Morris JC, Fulling KH, Gado MH. Periventricular white matter lucencies in senile dementia of the Alzheimer type and in normal aging. *Neurology.* 1987;37:1365-1368.

In Reply.—The significance of white matter and periventricular hyperintensities and the question whether they differ between patients with Alzheimer's disease and age-matched controls remains to be discussed. We found no difference between patients with Alzheimer's disease and normal subjects.[1] Fazekas and McDonald point out possible methodological bias we would like to discuss in the following nine points:

(1) We agree with them that including magnetic resonance imaging scans of lower quality for calculation of interobserver agreement might have lowered κ values in the evaluation of Fazekas' scoring system.[2] We have again calculated κ among the 27 high-quality magnetic resonance images and we found very small improvements (periventricular hyperintensity, 0.44 instead of 0.43; white matter hyperintensity, 0.58 instead of 0.50). Kozachuck et al[3] found higher values of κ than we did but most of their subjects had very low periventricular and white matter hyperintensity scores; we think that the interobserver reliability is more likely to be lower among subjects with such low scores. We have just finished (publication in process) a new study in 29 patients with Alzheimer's disease and 34 control subjects with high-quality magnetic resonance imaging to evaluate the intraobserver and interobserver reliability of a more elaborate rating scale. All magnetic resonance imaging scans were scored independantly by four of us (D.L., J.P.P., P.S., F.B.) using both rating scales; we compared them using Bland and Altman's method.[4] This study confirmed the poor intraobserver and interobserver reliability of Fazekas' scoring system and a moderate superiority of our new rating scale in spite of its complexity.[2] (2) An uneven level of magnetic resonance imaging interpretation skills among observers with different backgrounds may effectively have affected intraobserver and interobserver agreements in our study. In our new study the magnetic resonance imaging evaluations were performed by two neuroradiologists and two neurologists; the intraobserver agreements were better with radiologists (J.P.P., F.B.) but they did not significantly differ from those of neurologists (D.L., P.S.). (3) Fazekas' opinion that their simple scoring system will be more likely to yield good intraobserver and interobserver agreements than a complex one is not confirmed in our new study. Moreover, in a study of computed tomographic white matter changes in Alzheimer's disease,[5] we found a high level of intraobserver ($\kappa = 0.95$) and interobserver ($\kappa = 0.88$) agreements using the very elaborate scoring system of Rezek et al.[6] (4) We totally agree with Fazekas' opinion that observations of a minor role of white matter and periventricular hyperintensities in patients with Alzheimer's disease without cerebrovascular risk factors represent a true finding and do not reflect inadequacy of the scoring scheme. When our study was published, we were unable to affirm this, but now we have further information in accordance with Fazekas' opinion: in order to know the role of the scoring scheme, two of us who were not coauthors of the article (P.S., F.B.) reinvestigated, in another European University Hospital, our magnetic resonance imaging using their own scoring method[7] and they confirmed the lack of difference between patients with Alzheimer's disease and control subjects. (5) The reason why one third of subjects had technical difficulties in imaging is related to their neuropsychological impairments, since this was observed only in the group with Alzheimer's disease. This undoubtedly has led to a skewing of the population toward less affected subjects as suggested by McDonald; the mean Mini-Mental State Examination scores in this study were significantly higher than in other studies performed by our study group.(6) We agree with McDonald's opinion that possible problems secondary to small magnet size and large interslice gap might have occurred. However, the technique was the same between the two groups, and if we could have missed some hyperintensities, it would be balanced between groups. Of course, new generations of machines will avoid such problems in the future. (7) None of the 27 subjects included in the study had a history of mood disorders, according to a comprehensive discussion with a close relative. (8) We also agree with McDonald's opinion that we probably found no correlation between white matter and periventricular hyperintensity scores and Mini-Mental State Exami-

nation scores in patients or age in normal subjects since we have patients with high mean Mini-Mental State Examination scores. In our further study with 63 subjects, with larger ranges of Mini-Mental State Examination scores and ages, we found: (1) in control subjects a correlation between periventricular and white matter hyperintensity scores and age, and (2) in patients no correlation between periventricular and white matter hyperintensity and Mini-Mental State Examination scores, as reported by Kozachuck et al.[4] (9) McDonald's question whether early- and late-onset Alzheimer's disease might represent two different groups according to magnetic resonance imaging white matter changes cannot be answered from our recently published study,[1] since it included 14 patients with presenile Alzheimer's disease and only three patients with senile Alzheimer's disease. This question was recently investigated in our new study in 34 control subjects and 29 patients, all free of any possible vascular risk factor. We confirmed all our previous data, but only in presenile Alzheimer's disease (onset before age 65): we found no difference between patients with Alzheimer's disease and control subjects for both white matter and periventricular hyperintensities (16 patients with Alzheimer's disease and 15 control subjects; beta risks of type II errors, 0.15 and 0.03). However, in senile subjects (13 patients with Alzheimer's disease and 19 control subjects) white matter hyperintensities were significantly higher in Alzheimer's disease ($P < .01$; Mann-Whitney U test). Like us, Kozachuck et al[4] found no difference between patients and control subjects, and they probably have a predominance of presenile cases too, according to the mean ages of their patients. These new data point out the necessity to look at the mean age of the study population, and that matching patients and control subjects might not be sufficient. The age of the study population and whether they have senile or presenile dementia might have more importance than the scoring scheme to explain differences between the results of different studies.[7]

We are grateful to Fazekas and McDonald and their coworkers to give us the opportunity to discuss this point.

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2. Fazekas F, Chawluk JB, Alavi A, et al: MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJNR.* 1987;8:421-426.
3. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet.* 1986;1:307-310.
4. Kozachuck W, DeCarli C, Horwitz B, et al. White matter changes in dementia of the Alzheimer type (DAT) and healthy controls without cerebrovascular risk factors: an MRI study. *Neurology.* 1990;40:175. Abstract.
5. Leys D, Pruvo JP, Parent M, et al. Could wallerian degeneration contribute to 'leuko-araiosis' in subjects free of any vascular disorder? *J Neurol Neurosug Psychiatr.* In press.
6. Rezek DL, Morris JC, Fulling KH, et al. Periventricular white matter lucencies in senile dementia of the Alzheimer type and in normal aging. *Neurology.* 1987;37:1365-1368.
7. Scheltens PH, Barkhof F, Valk J, Algra P, Gerritsen van der Hoop R, Wolters EC. White matter lesions on magnetic resonance imaging in Alzheimer's disease and normal aging. *Neurobiol Aging.* 1990;11:263-264.

Third-Nerve Palsies and Angiography

To the Editor.—Aneurysmal compression of the third nerve produces an oculomotor nerve palsy with prominent pupillary involvement. Cerebral angiography is indicated in the workup of such third-nerve palsies if another cause is not promptly forthcoming. *Pupil-sparing* third-nerve palsies are often caused by local ischemia, and the risks of angiography are likely increased in such individuals. Unfortunately, occasional third-nerve pareses with limited pupillary participation *do* result from early aneurysmal compression,[1] presenting the clinician with a management dilemma.

A noninvasive test that could eliminate aneurysmal compression as the cause of a third-nerve palsy would be most valuable. Currently, lack of spatial resolution compared with conventional angiography and slow flow within the aneurysm preclude magnetic resonance angiography from replacing conventional angiography in the diagnosis of small cerebral aneurysms.[2] However, aneurysms that produce oculomotor nerve palsies should be relatively easy to detect: their sites of involvement are known and they are usually larger than 4 mm.[3]

Our recent experience with two patients who had acute third-nerve palsies involving the pupils is not encouraging. Spin echo magnetic resonance imaging and magnetic resonance angiography were performed using flow-related enhancement. The magnetic resonance angiography was acquired with the following techniques: TR = 52 milliseconds/TE = 11 milliseconds and a flip angle of 90° on a Philips 1.5 tesla magnet. Slice thickness was 3 mm, with a 1-mm overlap. The images were reformatted to three-dimensional images. Pre-excitation was used to suppress signal produced by flow in the opposite direction. We were unable to detect the anticipated posterior communicating artery aneurysms, which proved to be 5 and 6 mm in diameter at conventional angiography.

Magnetic resonance imaging of patients with third-nerve palsies will detect many of the causative aneurysms, but, at present, normal magnetic resonance imaging studies cannot rule out aneurysmal compression of the third nerve.

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2. Ross JS, Masaryk TJ, Modic MT, Ruggieri PM, Haacke EM, Selman WR. Intracranial aneurysms. *AJNR.* 1990;1:449-456.
3. Soni SR. Aneurysms of the posterior communicating artery and oculomotor paresis. *J Neurol Neurosurg Psychiatry.* 1974;37:475-484.

Editorial

Freeze the Ocean

The *Journal of the American Medical Association* and its family of specialty journals are addressing the issue of access to medical care. Matthew Menken presents a thoughtful look at this problem in a special article in this issue.[1] One of the major priorities in most industrialized nations is the provision of universal access to high-quality medical care at low cost. There have been varying degrees of success and many failures, and an ideal program has not been found. Certainly, the system in the United States has failed as there are millions of citizens who are underinsured or poorly insured. Basic desiderata just mentioned fall apart when other elements are deemed important, as instant and convenient access to care, free choice, unrationed care, finest technology, and adequate reimbursement for the providers (hospitals, physicians, nurses). There is then a trade-off, and, unfortunately in this country, it is universal access. Also, as Menken points out, the care even when available may not serve the patient's needs.

See also p 472.

The medical care in the United States when at its best is likely unparalleled anywhere in the world. Certainly, it is the most expensive by far. But consistently, in surveys done in industrialized countries of the world, we are the least satisfied with our health care system.[2] The dissatisfaction does not arise from the quality of care but from the fear that we may not have the insurance or sufficient insurance when it is required. A fear that is not shared with citizens of other countries surveyed.

The Canadian system of health care has the highest satisfaction rating by its own citizens. It is also the system most admired by United States citizens. Even in Britain, which has the lowest cost per capita for health care, the satisfaction rate is higher than in this country.

At this time when we are critically evaluating our own system with the possibility of more government involvement, both the Canadian and British systems are showing major stresses.

The Canadian government through the provinces is the single payer. The Canadian system saves a significant portion on administrative costs and global hospital budgeting.[3] Payment to individual physicians is less, but disparity in income is not great as overheads due to billing costs and malpractice insurance are considerably less.[4] Our idyllic view of the health system north of the border is now being questioned as more and more stresses appear in the Canadian system.[5] Long waits for services, inconvenient services, inadequate access to technology, lack of innovative delivery systems, and provider discontent are parts of the complaint. The transplantability of the system is also questioned, often along culture lines. A Canadian health official pointed out that Americans were paranoid about their government in that they did not trust it; on the other hand, the Canadians are schizophrenic in that they had a greater trust in government but felt the government went about it all wrong. However, there are many excellent features of their system such as global budgeting of hospitals and greater control of placement of expensive technology.

The British National Health System, again with universal access, has a fundamental difference from the Canadian system. The National Health System became both payer and provider by nationalizing the hospitals and employing the physicians. The system has evolved and has been modified since its inception in 1948. During the Thatcher years it came under increasing scrutiny, and in 1989 a government White Paper recommended major reforms.[6] Many of the proposed reforms had the government lessening its control over hospitals and practitioners. What will evolve from this is yet to be seen, but major concerns about restriction in services have already arisen.

No system seems to have the perfect solution as Menken, quoting Mencken, suggests in his special article.[1] It is likely that we all know what is needed and desirable. We can land a man on the moon and put a bomb down a chimney from 10 000 feet, but these projects pale when we deal with the multifarious and diverse elements of the health care system. We are in the situation of the admiral who was asked what to do about the U-boat threat. He replied immediately, "Freeze the ocean. Those on the top can't go down, and those on the bottom can't come up." When asked how this would be accomplished, he replied, "I just set the policy, you work out the details." It is the details that will be difficult.

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References

1. Menken M. Caring for the underserved: health insurance coverage is not enough. *Arch Neurol.* 1991;48:472-475.

2. Blendon RJ, Leitman R, Morrison I, Donelan K. Satisfaction with health systems in ten nations. *Health Affairs.* Summer 1990;185-192.

3. Evans RG, Lomas J, Barer ML, Labelle RJ, et al. Controlling health expenditures: the Canadian reality. *N Engl J Med.* 1989;9:571-577.

4. Fuchs VR, Hahn JS. How does Canada do it? A comparison of expenditures for physicians' services in the United States and Canada. *N Engl J Med.* 1990;323:884-890.

5. Iglehart JK. Canada's health care system faces its problems. *N Engl J Med.* 1990;322:562-568.

6. Lister J. Reform of the British National Health Service. From White Paper to Bill in Parliament. *N Engl J Med.* 1990;322:410-412.

Caring for the Underserved

Health Insurance Coverage Is Not Enough

Matthew Menken, MD

The President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research stated in 1983 that "Society has a moral obligation to ensure that everyone has access to adequate care without being subjected to excessive burdens."[1] By this measure, the health system of the United States is failing, since millions of citizens are unable to obtain necessary care each year. This is a paradox, given the large annual medical care expenditures in the United States. In 1991, such expenditures will exceed $600 billion, or 11.5% of the gross national product, an average of $2500 per capita. Comparative health care figures reveal that the United States spends per capita 38% more money than Canada, 88% more than West Germany, and 124% more than Japan. Moreover, expenditures in the United States are rising rapidly. Between 1980 and 1987, health expenditures in the United States increased from $248 billion to $500 billion, an increase of 102% during this brief period.[2]

See also p 471.

I suggest that the proportion of the gross national product now spent on health care in the United States is probably more than sufficient to provide comprehensive care for all people, including the provision of effective and high-quality medical care for those people presently underserved.[3] No other country has such readily available technology, an equivalent density of well-trained physicians in 24 specialties, or the institutional resources needed for first-rate medical care. American biomedical and health services research is generally acknowledged to be a bigger and better enterprise than anywhere else. A major deficiency is the system's failure to provide care for approximately 37 million people, or 15% of the population, who are unable to afford private insurance and are also ineligible for publicly funded programs.[4] Contrary to popular belief, nearly three fourths of these uninsured citizens are working Americans and their families, and more than two thirds are white. Only 40% of all of our citizens below the poverty level (including many children) are insured through Medicaid, a program ostensibly designed for the poor. Given this disturbing evidence, it is not surprising that public opinion polls find many US citizens dissatisfied with their health care system. There is little doubt that health care access and cost are the major issues of concern for most of these Americans.

BARRIERS TO ACCESS

Since cost is only one of the barriers to access for high-quality care, the total number of underserved people greatly exceeds the number of uninsured and underinsured. For example, many health indicators demonstrate a disparity among people of different racial and ethnic groups that cannot be ascribed entirely to cost. In 1987, the age-adjusted death rate for stroke among the black population was nearly twice that of white people, while the infant mortality rate for black infants (17.9 per 1000 live births) was more than twice the rate for white infants (8.6 per 1000 live births). About 79% of white mothers began prenatal care in the first trimester, compared with 61% of black and American Indian mothers.[5]

Such data suggest that, although cost is an important barrier to health care for many Americans, other access barriers may be paramount for some people. For example, geographic barriers are important for many rural families. In 1985, there were 53 physicians per 100 000 people in US counties whose total population was less than 10 000, compared with a national average of 165 physicians per 100 000 people. Geographic and language barriers, and the "culture of poverty," are also important problems in access in blighted urban areas where the mortality rate for adult black men exceeds that of some developing countries. Between 1963 and 1980, office-based physicians in such urban areas declined 45%.[6] With the exception of some adult and pediatric training programs in hospitals that emphasize culturally appropriate care, there is a consensus that inner-city hospital–based care is often more impersonal and less culturally sensitive than office-based care, especially when such care is provided by minority physicians.[7]

Furthermore, medical care is only one factor in the determination of health status, which also depends on many other sociocultural parameters. Sanitation, the quality of the food supply, the level of education in the community, among other factors, influence personal health status. If medical care were the only determinant of health, and cost the only access barrier, then one would anticipate that a cost-free health care system, as under the National Health Service in

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the United Kingdom, would demonstrate health status equality for all population groups. Many studies in the United Kingdom conducted over two decades have demonstrated a robust negative association between social class (often called socioeconomic status in the United States) and all-cause mortality.[8] The lower the social class, the greater the mortality. This remarkably consistent finding occurs at all levels of society, and it is not limited only to those people who are overtly poor and deprived. For example, individuals in upper managerial roles and their families have a lower rate of all-cause mortality than do those in middle-management roles and their families. The same negative correlation has been observed for many medical and neurological disorders such as coronary artery disease, stroke, and many forms of cancer.[9]

Such data suggest that solving the problem of caring for the "uninsured and underinsured," although certainly of great importance, is not coextensive with the larger and more difficult task of caring for the underserved, as might be implied by the rubric of this theme issue of the ARCHIVES under which this article is subsumed. The conventional wisdom notwithstanding, individual physicians and the American Medical Association should make it clear to policymakers that insurance reform and financial measures alone, now as in the past, will likely fail to solve the twin societal goals of caring for the underserved and further improving care quality. In 1929, when national expenditures of $3.6 billion, or $30 per capita, were already a source of great public concern, the prestigious Committee on the Costs of Medical Care discovered "much waste" in such features of the health system as payments for ineffective medications, uncoordinated private practices, and inefficiently used hospitals. This Committee called for changes in the organization and patterns of delivery of medical care as the appropriate way to control costs, ". . . in view of the widespread lack of needed medical care. . . ."[10]

It remains unchanged after more than half a century that many factors that contribute to differences in health status as a reflection of the social stratification of society and the material aspects of living, such as housing, education levels, and working conditions, are not readily influenced by medical interventions, however accessible. The same public resistance to provide necessary resources for neuroscience research and the medically underserved applies also in the case of the nutritionally underserved, the housing underserved, and the educationally underserved. There are an estimated 2 million homeless people in the United States, and 20 million illiterate adults. For these people, a more humanitarian system of financing medical care would obviously be beneficial, but much more needs to be done. Clearly, the mitigation of poverty (especially child poverty), homelessness, and social deprivation can contribute greatly to improved national health indicators and the relief of human suffering. Given the focus of national attention on the cost of care, it should be underscored repeatedly that caring for the underserved and caring for the uninsured and underinsured are qualitatively different conceptualizations for public policy.

CARING FOR THE UNINSURED AND UNDERINSURED

Given the multifaceted and labyrinthine problems of the underserved, it is not surprising that proposals to mitigate the lack of health insurance abound, whereas the broader care crisis among the underserved has received much less attention.[11] It seems likely that even these more limited proposals will face rough sailing in the political arena. On July 1, 1988, President Reagan signed the Medicare Catastrophic Coverage Act of 1988, the largest expansion of federal involvement in health care since 1965, when the Social Security Amendments of 1965 (Medicare and Medicaid) were first implemented. Unlike prior policy that paid for coverage out of general tax revenues, the 1988 law required that the wealthier beneficiaries pay an income tax surcharge, and that all beneficiaries pay an additional $4 in the basic Medicare part B monthly premium. Although mandated benefits under this law were quite generous, the constituency of the American Association of Retired Persons opposed this measure vigorously. Fearing political fallout, Congress hurriedly repealed the law altogether, leaving those senior citizens without supplementary private insurance more vulnerable than ever to increasing medical bills.[12]

The many proposals for improving insurance coverage reflect a consensus that something needs to be done, but a controversy about what to do.[13,14] A proposal by Physicians for a National Health Program calls for a national health insurance program modeled on the system in Canada, with a single public insurance payor for all health care, and a predetermined annual cap on payment to hospitals.[15] Another proposal, the Consumer Choice Health Plan, would convert all insurance plans to prepaid coverage, and would require employers to purchase insurance for employees' health care from competing managed care plans.[16] The National Leadership Commission on Health Care proposal would provide health care for the uninsured through a state-based program funded by government, employers, and beneficiaries (on the basis of income), and would include an expanded technology assessment and outcome evaluation effort.[17] The American Medical Association has presented a 16-point proposal, *Health Access America*, that includes reform of Medicaid, Medicare, and professional liability, also requires employer provision of health insurance, and would create state-run risk pools for the uninsured.[18]

CARING FOR THE UNDERSERVED

H. L. Mencken is reputed to have said that for every complex human problem there is a solution that is simple, elegant, and wrong. What is generically problematic with many proposals for health system reform is a viewpoint sharply focused on health insurance and cost. This focus on selected aspects or abstractions of an actual situation or problem, while ignoring other factors of relevance, is an example of a common source of logical error in many scientific fields, which has been called the Fallacy of Misplaced Concreteness.[19] I would suggest that the American Medical Association's framework for change is exceptional and noteworthy, in part because it lends itself more readily than most other proposals to such structural and procedural changes in the delivery of medical services as may be needed to provide better care for the underserved. Caring for the uninsured and underinsured is an important first step, but equity and social justice in health care also require caring for all of the underserved. As an additional step toward resolution of this problem, I would propose the following measures as ones that merit thoughtful and open-minded discussion.

First, efforts to improve the scientific underpinning of medical care must be expanded, as a logical step toward prevention of disorders that rely for treatment on expensive "halfway" interventions. For example, it has been estimated that mortality from metastatic female breast cancer can be reduced 30% by regular breast examination and mammography performed at recommended intervals.[20] Moreover, about 30% of total Medicare hospital expenditures are on behalf of patients in the last year of life, mostly the last 6 months, many of whom suffer from Alzheimer's disease and other dementias. Given the large cost of services for patients with dementia, and a prevalence of Alzheimer's disease of nearly half of all people older than 85 years of age (the most rapidly growing segment of the US population), it is astonishing that research funding for this disorder amounts to only 0.15% of the costs of care.[21,22]

Although *Health Access America*, the AMA's health care proposal, correctly calls for the expansion of biomedical research, a broader paradigm of research is necessary to provide comprehensive care for the underserved. As I have suggested previously, amplification of the investigative effort should logically include much more research in the social and behavioral sciences relevant to human health and disease,[23] as well as an expanded health services research agenda to foster intersectoral cooperation with workers in such fields as nutrition, education, and housing.[24] Such health services research activity in the recent past has included an expanded effort to measure the appropriateness and effectiveness of medical care, an examination of health system administrative costs and the effects of reimbursement reform, as well as "the technology of patient experience" (outcomes research), as in the recent initiatives of the American College of Physicians and the Public Health Service's Agency for Health Care Policy and Research.[25-27]

Second, the absolute number and relative proportion of primary care physicians must be expanded. The President of the Association of American Medical Colleges has noted that ". . . our academic medical centers will lose vital national and public support if they do not respond to society's desire for more primary care physicians."[28] Of all physicians in the United Kingdom, Canada, and the United States, 70%, 50%, and 30%, respectively, are generalists. In my view, solving the crisis in primary care is an essential component of any solution to the problem of caring for the underserved in the United States. Put another way, most of the care requirements of the underserved fall within the domain of primary care medicine. Hence, providing adequate insurance for all people cannot be expected to correct the mismatch between actual health needs and the specialty distribution of physicians. This keystone issue is one that often goes unnoticed or unsupported by many neurologists and other specialists. It is a question of our orientation and commitment to provide high-quality medical care for individual patients, without a concomitant awareness of those people who are not receiving care, as well as the differential burden of illness in the entire population to be served. This is an example of what has been called the *Inverse Care Law*, which holds that market forces cause medical care to vary inversely with the need for it in the population to be served.[29]

What is needed to address this issue, first of all, is a major initiative to recruit minority health professionals and strengthen minority medical institutions. Among 15 433 senior medical students in 1989 through 1990, only 826, or 5.3%, were black. (As of September 1, 1989, there were only 29 black neurology residents on duty, including one child-neurology resident.) Moreover, special measures are needed to recruit talented students from rural and other underserved areas, since these individuals are more likely to establish primary care practices where they are most needed.[30] Perhaps it is time to reform the criteria by which candidates are selected for enrollment in medical school. Each medical school might set its own arbitrary *threshold level* of academic grades and examination scores that all candidates must surpass, but once that is done, grades and scores no longer matter in the selection process for those individuals who exceed the cutoff level.[31] Finally, is there any doubt that the framework for physician payment and professional liability needs to be modified so that doctors can care for the underserved without great risk to their personal and family's financial security?

Third, medical schools need to develop appropriate community-oriented learning experiences for all medical students. In terms of faculty prestige and status, students learn that the "ins" are in (hospital based), and the "outs" are out (ambulatorium). Some schools have experimented with educational programs in health maintenance organizations, community health centers, and other facilities. It is also a question of decentralizing a health system that preferentially directs resources to surgical and procedural interventions carried out in hospitals, leaving community-based and preventive services seriously underfunded. Given the widespread dissatisfaction of many people with the health system, and the declining number of applicants to American medical schools, health science centers need to identify the task of medicine, in its broadest sense, for all students and residents, as well as the role of the doctor in an industrialized society. We seem to have forgotten that scientific expertise and technical competence are not the foundations of patient satisfaction in many situations. When learning is exclusively carried out in teaching hospitals, students sometimes get the erroneous impression that caring is what is left for doctors to do when curative medicine has failed.

In terms of caring for the underserved, learning experiences in the community will heighten student and resident awareness of local priority health problems based on sound epidemiological principles, as in the educational model developed by an international task force commissioned by the Network of Community-Oriented Educational Institutions for Health Sciences.[32] Such "real life" experiences, in which students live and learn in selected community settings, are likely to foster the linkage between knowledge and skills, on the one hand, and the concept of social responsibility, on the other, so that all students understand why the social role of every doctor, regardless of the field of specialization, must extend beyond the care of individual patients.

CONCLUSIONS

In May 1977, the Thirtieth World Health Assembly resolved that "the main social target of governments and the World Health Organization in the coming decades should be the attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life."[33] To achieve this goal in the United States, expanding insurance coverage for the uninsured and underinsured is an important step. However, the many barriers to care other than cost, and the limited role of medical care as a determinant of the overall health status of the population, call for a more comprehensive framework for reform that views health care for all of the underserved in its social context.

I suggest that the proposal of the American Medical Association, *Health Access America*, might be modified and enlarged to address these concerns. The expansion of the biomedical research agenda should be matched by a much larger research effort in the social and behavioral sciences relevant to human health and disease, as well as the health services research agenda. The mismatch between the specialty distribution of physicians and the health needs of the entire population to be served calls for an increase in the number and proportion of primary care physicians, and the recruitment of a larger number of minority medical students. Finally, all medical students should have active learning experiences in a community-oriented framework of service provision to ensure that future generations of physicians understand the role of medical care for population groups as well as individual patients. Together, such changes signify the addition of relevance to the equation of access, cost, and quality in caring for the underserved.

References

1. President's Commission for the Study of Ethical Problems in Medical and Biomedical and Behavioral Research. Report: The ethical implications of differences in the availability of health services. Washington, DC; March 1983;1:22.
2. Politser P, Cunico E. *Socio-Economic Factbook for Surgery 1989*. Chicago, Ill: American College of Surgeons; 1989.
3. Wennberg JE. Outcomes research, cost containment, and the fear of health care rationing. *N Engl J Med*. 1990;323:1202-1204.
4. Braveman P, Oliva G, Miller MG, Schaaf VM, Reiter R. Women without health insurance: links between access, poverty, ethnicity, and health. *West J Med*. 1988;149:708-711.
5. National Center for Health Statistics. *Health, United States, 1989*. Hyattsville, Md: Public Health Service; 1990.
6. Kindig DA, Movassaghi H, Dunham NC, Zwick DI, Taylor CM. Trends in physician availability in 10 urban areas from 1963 to 1980. *Inquiry*. 1987;24:136-146.
7. Gessert C, Blossom J, Sommers PS, Canfield MD, Jones C. Family physicians for underserved areas: the role of residency training. *West J Med*. 1989;150:226-230.
8. Morris JN. Inequalities in health: ten years and little further on. *Lancet*. 1990;336:491-493.
9. Bunker JP, Gomby DS, Kehrer BH. *Pathways to Health: The Role of Social Factors*. Menlo Park, Calif: The Henry J. Kaiser Family Foundation; 1989.
10. Falk IS, Rorem CR, Ring MD. *The Costs of Medical Care*. Chicago, Ill: The University of Chicago Press; 1933; 592-593.
11. *Education of Physicians to Improve Access to Care for the Underserved*. Hyattsville, Md: Health Resources and Services Administration, US Dept of Health and Human Services; 1990.
12. Ahluwalia JS. Health care in the United States: our dynamic jigsaw puzzle. *Arch Intern Med*. 1990;150:256-258.
13. Kinzer DM. Universal entitlement to health care: can we get there from here? *N Engl J Med*. 1990;322:467-470.
14. Rockefeller JD. The Pepper Commission report on comprehensive health care. *N Engl J Med*. 1990;323:1005-1007.
15. Himmelstein DU, Woolhandler S. A national health program for the United States. *N Engl J Med*. 1989;320:102-108.
16. Enthoven A, Kronick R. A consumer-choice health plan for the 1990s. *N Engl J Med*. 1989;320:94-101.
17. Relman AS. The National Leadership Commission's health care plan. *N Engl J Med*. 1989;320:314-315.
18. American Medical Association. *Health Access America*. Chicago, Ill: American Medical Association; February 1990.
19. Whitehead AN. *Science and the Modern World*. New York, NY: Macmillan Publishing Co Inc; 1962:75.
20. Amler RW, Dull HB. *Closing the Gap: The Burden of Unnecessary Illness*. New York, NY: Oxford University Press Inc; 1987.
21. Moss M, Alpert M. Alzheimer's disease and other dementing disorders. In Alpert M, Moss M, eds. *Geriatric Neuropsychology*. New York, NY: Guilford Press; 1988:145-178.
22. Weiler PG. The public health impact of Alzheimer's disease. *Am J Public Health*. 1987;77:1157-1158.
23. Menken M. The changing paradigm of neurologic practice and care: implications for the undergraduate curriculum. *Arch Neurol*. 1990;47:334-336.
24. Schaefer M. Home and health: on solid foundations? *World Health Forum*. 1990;11:38-45.
25. Ellwood PM. Outcomes management: technology of patient experience. *N Engl J Med*. 1988;318:1549-1556. Shattuck lecture.
26. Ginsburg JA, Prout DM. Access to health care. *Ann Intern Med*. 1990;112:641-661.
27. Clinton JJ. From the Agency for Health Care Policy and Research. *JAMA*. 1990;263:2158.
28. Petersdorf RG. Medical education. *JAMA*. 1990;263:2652-2654.
29. Hart JT. The inverse care law. *Lancet*. 1971;1:405-412.
30. DeFriese GH, Ricketts TC. Primary health care in rural areas: an agenda for research. *Health Serv Res*. 1989;23:931-973.
31. Antonovsky A. Medical student selection at the Ben-Gurion University of the Negev. *Isr J Med Sci*. 1987;23:969-975.
32. Neufeld VR, Bearpark S, Winterton C. Optimal outcomes of clinical education. In: Gastel B, Rogers DE. *Clinical Education and the Doctor of Tomorrow*. New York, NY: New York Academy of Medicine; 1989:11-23.
33. World Health Organization Regional Office for Europe. *Targets for Health for All*. Geneva, Switzerland: World Health Organization; 1985.

Access to Health Care

One Neurologist's Perspective

Michael P. Earnest, MD

• Millions of residents of the United States have difficulty obtaining health care. Barriers impeding access to care include poverty, physical unavailability of health care services, absence of health insurance, and physicians unwilling to care for uninsured patients. Many patients do not successfully use health services because of educational, cultural, and language barriers. A major access barrier is lack of health insurance. Over 30 million people in the United States have none, the so-called medically indigent. Among them are over 3 million people with neurologic disorders. They have additional barriers to overcome because often they cannot work, cannot drive, have difficulty using public transportation, and have major cognitive and communication impairments. Medical and governmental bodies are debating solutions to the health care access crisis. Physicians should actively participate in this national debate. Neurologists should address the special needs of patients with neurological disorders.

(*Arch Neurol.* 1991;48:476-479)

A 52-year-old laborer had a long history of poorly controlled hypertension. A stroke at age 40 years caused a mild left hemiparesis, but he was able to continue working parttime and he was fully independent in his daily living. He had no health insurance and no savings. He had last seen a physician at a public clinic but admitted he had not taken the antihypertensive medications that had been prescribed. He admitted to prior heavy alcohol use but denied any alcohol use since the stroke.

Three days before his admission on December 5, 1990, while at home, he had sudden vertigo, nausea, and vomiting and then fell. He could not recall subsequent events but was found 48 hours later still on the floor, conscious but confused and unable to get up because of a severe left hemiparesis. He was taken by ambulance to a private hospital, where he was treated in the emergency department. A computed tomographic scan showed an old right-sided cerebral infarct. Twelve hours later, he was transferred to Denver (Colo) General Hospital and was admitted. The patient stated he was transferred because "I didn't have any money."

During this hospitalization, he was in the intensive care unit 18 days for management of severe hypertension, aspiration pneumonia, respiratory failure, recurrent chest pain, and thrombophlebitis. He had a gastrostomy because of dysphagia and aspiration. After 30 days, he was transferred to the rehabilitation unit. The total bill for the 30 days was $61 185.

Five weeks later his left arm remained totally paralyzed. He could take a few steps using a walker and a leg brace and with assistance. He was still fed by gastrostomy. He remained in the rehabilitation unit. He was not expected to return to work and so had applied for welfare assistance and Medicaid. The rehabilitation staff expected he would have to stay at least several weeks in a nursing home. He hoped eventually to resume independent living and to be able to swallow food again.

Many residents of the United States have difficulty obtaining needed health care (Table 1).[1,2] Growing concern about barriers between patients and health care has prompted numerous governmental and medical reports on inadequate access to health care, the effect of this on health status, and possible solutions to the problem.[3-6]

FACTORS AFFECTING ACCESS TO HEALTH CARE

An individual's access to health care depends on several interrelated factors that fall into the following four principal categories: financial, health care system, personal/cultural, and social system.[7,8] The financial determinants of access to care are health insurance (eg, private or employer-based insurance or Medicare/Medicaid coverage) and personal cash reserves to pay the expected bills, medication prescriptions, and related costs, including transportation. Access to the health care system is determined by the physical availability of a physician, clinic, or hospital[6] and the capacity or willingness of those providers to see the patient. Personal and cultural determinants of access are the characteristics of the patient that enable successful acquisition of health care services. Education, ability to speak and read English, attitude toward health and health care, and cognitive ability are all important. Social system access to Medicaid or other public assistance programs for health care depend on availability of state and federal programs and accessible entry systems, including local offices.

A sick person can obtain health care services if there is a physician's office or other health facility available, the patient has sufficient insurance or cash, is motivated to seek care, and can communicate with the provider about the illness. However, multiple barriers pre-

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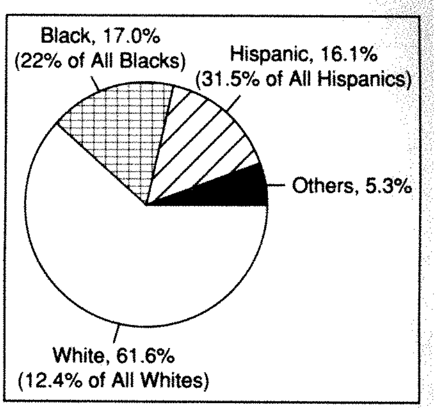
Reprints not available.

Table 1.—Percentage of 10 130 Respondents Reporting Difficulty Obtaining Health Care*

Type of Difficulty	%
People with chronic or serious illness who had no physician visit in prior 12 months	18.5
Needed care but had difficulty obtaining it	16.1
Pregnant women without care in first trimester	15.8
Economic barriers to receiving health services	7.8
Tried to get care but could not, for financial reasons	0.4

*Adapted from Robert Wood Johnson Foundation Special Report.[1]



Uninsured US population by race (from King[3]).

vent many US citizens from receiving needed care. Poverty, lack of health insurance, absence of physicians and clinics in rural and inner-city areas, low level of education, inability to speak or read English, and intimidating health system and social services bureaucracies all create barriers between many people and health care.[1,7-10]

People with neurological disorders may have even more difficulty obtaining health care than do others. The author's clinical experience in an urban municipal hospital indicates that patients with dementia, stroke, Parkinson's disease, multiple sclerosis, and epilepsy have special problems obtaining health care. Those diseases often cause loss of jobs, inability to obtain health insurance, problems driving a car or using public transportation, and impaired mental and communication ability, all of which interfere with obtaining health care. Public assistance programs, such as Medicaid, offer only partial relief of the financial problems, but the other problems remain formidable.

THE NATIONAL PROBLEM OF MEDICAL INDIGENCY

Because the United States has no universal health insurance system, individuals here must pay for medical care through personal health insurance or with out-of-pocket cash. Absence of health insurance is a major barrier to obtaining health care in our nation.[1,3,6,9,11] More than 30 million people under the age of 65 years have no health care insurance.[3,11] Estimates of this "medically indigent" population are as high as 37 million, about 15% of the US population.[3] This group has substantially increased during the last two decades.[1,3,11] Over half of these people are employed or are dependents of full-time employees; many others are the poor who are not eligible for Medicaid.[3,11] About 62% are non-Hispanic whites, 17% are black, and 16% Hispanic (Figure).[3,12] Ten million of the medically indigent are under the age of 19 years.[3]

Why do so many people have no health insurance? Federal and state health insurance systems cover many segments of the population. Medicare covers those over 65 years old and some chronically disabled people. Medicaid covers many impoverished pregnant women, mothers with dependent children, and most impoverished chronically disabled adults. However, state-funded Medicaid programs do not cover many people below the poverty level.[3,5] Also, many young people just entering the work force have no insurance for themselves or for their families.[3] Because of high premium costs, many employers, especially small and service-industry companies, offer no health insurance benefits.[3,11] Self-employed workers can purchase insurance, but many cannot afford the high price. All of these gaps in health insurance coverage combine to create the huge medically indigent population.

A consensus is growing among political and medical leaders that the absence of health insurance prevents people from receiving needed health care.[1,3,6,13] Long-term effects of reduced access probably are higher morbidity and mortality for uninsured people.[14,15] The excess morbidity and mortality increase unemployment and increase expenditures of public funds for the health-impaired population.[13] Widespread lack of health insurance is a major economic issue, not just one of social justice.

NEUROLOGIC DISORDERS AMONG THE MEDICALLY INDIGENT

The prevalence and incidence of neurological disorders among the medically indigent have not been studied. Kurtzke[16] estimated that neurologic disorders affect about 9.5% of the entire US population, ie, a point prevalence rate of 9500 per 100 000. Extrapolating that figure to the 34 million medically indigent, 3.2 million people have neurologic disorders. Using his estimates for prevalence of specific disorders, 272 000 people have cerebrovascular disease or transient ischemic attacks, 221 000 have epilepsy, 100 000 have lumbosacral herniated disk, 85 000 have cerebral palsy, 85 000 have dementia, and 68 000 have Parkinson's disease. Using Kurtzke's annual incidence figure, 850 000 medically indigent people develop a neurologic disorder within a given year.[16] Many of those patients need both acute and continuing neurological care.[17]

An additional large but unquantified number of cases of the acquired immunodeficiency syndrome (AIDS) exist among the medically indigent, and the prevalence of cases is still increasing. Employed people with AIDS eventually lose their jobs and then their health insurance, becoming medically indigent. Neurologic complications occur in over half of the people with AIDS,[18] so neurologic consultations, computed tomographic and magnetic resonance scans of the brain, and other neurologic tests often are needed.

NONFINANCIAL BARRIERS TO HEALTH CARE

Regardless of employment and insurance status, many patients in rural areas and in large inner-city poverty tracts have no access to care because physicians, clinics, and hospitals are not located there. Those patients must travel longer distances and incur higher costs in transportation and time to seek medical care. The physical and cognitive disabilities associated with neurologic diseases create even more problems traveling to distant clinics. The poor face other important access barriers.[7-10] Limited education, especially about health, leads to delay in seeking acute care, inattention to preventive services (eg, detection and treatment of hypertension to prevent stroke), and noncompliance with medical instructions and medication usage. Language barriers interfere with access for Spanish-speaking, Asian, and other non–English-speaking patients. Cultural values that deny illness or values that emphasize traditional healing methods may interfere with proper use of available medical care. The high prevalence

Table 2.—Features Common to Many Proposals for Providing Health Insurance to All US Citizens

Expand Medicaid to include the poor currently not covered
Mandate that employers provide health insurance to all employees
Establish state insurance "pools" to cover those "uninsurable" because of severe medical conditions
Develop insurance to pay for catastrophic illness and long-term care

of alcohol and other substance abuse and of severe mental illness in inner-city poor populations compounds the educational and cultural factors.[19]

Even middle-class, educated, insured patients are facing more barriers to neurologic care. Managed-care systems, trying to limit utilization and hold down costs, discourage primary care physicians from referring patients to specialists (eg, neurologists) and from ordering expensive tests, including computed tomographic and magnetic resonance scans. Hospital admissions are being limited by utilization-review plans and lengths of hospital stay controlled by diagnosis related group reimbursement. How much these mechanisms deny access to needed health services is unclear. Nonetheless, even though the purpose may be laudable, they are barriers between patients and health care services, including neurological services.

WHO TREATS THE ACCESS-POOR PATIENTS?

Most patients with limited access to medical care are treated in public clinics and hospitals and in urban teaching hospitals, both public and private. The "general hospital" and its clinics have long been the "safety net" for meeting health needs of the urban Medicaid and uninsured population.[6,20] However, these facilities are under extreme financial and political pressure.[21,22] Emergency departments, clinics, and wards are strained to the point that an acceptable quality of care often is compromised.[6] Reduced reimbursements from Medicaid, increasing numbers of uninsured patients, the epidemics of AIDS, drug abuse, and violence in the inner cities, and increased hospital operating costs have driven many public and private teaching hospitals deeply into debt.[21,22] Some have even closed.[21,23] Those that remain open are short-staffed and overcrowded.

Physicians in their private offices and hospitals have traditionally cared for many Medicaid and medically indigent patients. However, inadequate Medicaid and other governmental reimbursement, rising overhead costs, fear of malpractice liability and decreased ability to shift costs from the "no-pay" to the "full-pay" patients have forced private physicians and hospitals to reduce charity care. Now, they give emergency care and then arrange further treatment at a public agency,[21,24] the practice commonly termed "dumping."

With the private sector giving less charity care and the public sector unable to keep up with the increasing demand, indigent patients suffer even more. In the author's hospital and clinics, waiting times for visits have increased, heavy patient copayments have been instituted (eg, $250 for elective surgery), clinic hours have been reduced, and, now, discussion of reducing or even discontinuing major services has begun (eg, pediatrics and mental health). These steps are intended to increase revenues and decrease expenses, but they all create further barriers to access.

PROPOSALS TO SOLVE THE NATIONAL HEALTH CARE CRISIS

Numerous reports and plans have been published by governmental commissions, private study groups, and medical associations proposing steps to resolve the health care access crisis.[3-6,13,25-27] Several features are common to many proposals (Table 2). First, they propose that the Medicaid program should be expanded to cover all people below the federal poverty level who currently are uninsured. The uninsured poor with incomes above the poverty level could enroll in Medicaid by paying a graduated premium based on income. Second, the working uninsured would be covered by employer-sponsored health insurance. Small business employers would be given tax incentives, thus reducing their cost for providing insurance. Third, state-sponsored insurance pools would cover the "uninsurable" population, people with chronic costly diseases who cannot obtain insurance and who also are not eligible for Medicaid. Finally, long-term care and catastrophic illness coverage would be provided.

Other proposals advocate a federal government–sponsored national health insurance plan, possibly based on the Canadian health insurance system.[28] Several states, among them Massachusetts, Hawaii, and New York, have established statewide universal health insurance plans.[29] Some proposals advocate community action and more donated charity care by hospitals and physicians.[30,31]

In spite of the numerous commissions, studies, and proposals, major obstacles to any national solution exist. The first is the extraordinarily rapid growth in costs of health care and the corresponding growth of health care insurance premiums. Expenditures for health care in the United States grew from $75 billion in 1980 to nearly $500 billion in 1987 (*Am Med News.* Jan 12, 1990:25-26).[32] Health care expenses escalated from 7.4% of the gross national product in 1970 to 11% in 1988. Any solution to the health insurance crisis must include provisions to pay for implementing the plan and must include steps to restrict the rapid growth in health care costs. Illustrating the costs involved, expansion of the federal Medicaid program to cover the currently uninsured poor would cost between $9 and $35 billion, the exact amount depending on the services covered and the population included.[33]

Efforts to curb costs include "rationing" or "prioritizing" care by setting limited benefit packages,[13] requiring patient copayment, imposing managed care plans in which primary care providers act as "gatekeepers" between patients and high-cost care, and second opinions for high-cost procedures. Unfortunately, these cost-cutting measures are also barriers between a patient and health services.

The problem of cost also leads to contradictory public opinions about health care. Polls indicate that we want everyone, even the poor, to have access to health care (*Am Med News.* July 27, 1990:6).[34,35] We also want access to the latest, most expensive tests and treatments. Yet we do not want increased taxes or cuts in nonhealth programs to pay health care costs for the medically indigent (*Am Med News.* July 27, 1990:6).[34,35]

Even if a comprehensive nationwide health insurance plan were enacted, other access barriers would remain. Limited access would persist because of inequitable distribution of health providers and because of the educational, cultural, and social factors.

WHAT CAN PHYSICIANS DO?

Individual physicians cannot solve the health care access problems for over 30 million uninsured or for the comparably large Medicaid population. However, a physician can treat an individual person who needs care. Physicians in private practice, especially specialists (eg, neurologists) who may only need to perform a diagnostic consultation and then see the patient again a few times, can help by accepting uninsured and Medicaid patients. The editor of the *Journal of the American Medical Asso-*

ciation encouraged such professional commitment.[30] Physicians who work in municipal hospitals, public clinics, and teaching hospitals can help by continuing to provide as much high-quality, readily accessible care as is possible. Private and public physicians alike can urge administrators and boards of their hospitals and clinics to remain fully available and responsive to the needs of patients who come for care. At the same time, all physicians can limit health care costs for individual patients, and collectively for all of society, by charging reasonable fees, ordering tests prudently, and managing cases in a cost-effective fashion.

At the community level, physicians and medical societies can donate services to public clinics and hospitals. They can establish voluntary free clinics to give care to people with no other resources. They can work with community groups concerned about the problems of medical indigency, long-term care, cost of health care, and related issues.[31] Neurologists can advocate, with special authority, provision of services for people with chronic neurologic impairments, especially those in the medically indigent population.

On the state and national levels, organized physician associations can educate legislatures and governmental agencies about the health needs of the indigent and recommend programs to improve access to health care. Specialty societies, including neurologic societies, can develop plans focused on the needs of their specific patients. They can publicize those programs through the press and their own publications. The American Medical Association, American Society of Internal Medicine, American Academy of Pediatrics, and American College of Physicians, among others, have developed specific proposals.[4,5,7,26,36,37] The American Academy of Neurology has created a Task Force on Access to Health Care to study access and economic issues for patients with neurologic disorders.[38] Professional associations can also speak out on behalf of adequate funding for the health care agencies that provide care to the indigent and Medicaid populations.

COMMENT

Access to health care has become more difficult for tens of millions of people in the United States, many of whom cannot obtain needed health care. More than 3 million among that population have neurologic disorders. The long-term consequences of inadequate access to care cannot be predicted, but clinical common sense and available research studies indicate that the consequences will be higher morbidity and mortality in the medically indigent population. Exploding costs and widespread opposition to spending more on health care both preclude "quick-fix" solutions to the problem. Many different proposals have been made, and state legislatures and Congress are debating the issues.

Under any future national health plan, physicians will provide the health care. We should take an active part in the national debate on access to that care. Neurologists should speak out for the needs of patients with neurologic disorders, including the special needs of those among the medically indigent.

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References

1. Robert Wood Johnson Foundation Special Report. *Access to Health Care in the United States: Results of a 1986 Survey.* Princeton, NJ: Robert Wood Johnson Foundation; 1987.

2. Aday LA, Fleming GV, Andersen R. *Access to Medical Care in the US: Who Has It, Who Doesn't.* Chicago, Ill: Pluribus Press; 1984.

3. King M. *Medical Indigency and Uncompensated Health Care Costs.* Denver, Colo: National Conference of State Legislatures; 1989.

4. American Academy of Pediatrics. *AAP Special Report: Barriers to Care: Why Millions of Children Live in the Shadows, Unable to Receive Appropriate Health Care.* Elk Grove Village, Ill: American Academy of Pediatrics; 1989.

5. American Medical Association. *Health Policy Agenda for the American People: The Final Report of the Ad Hoc Committee on Medicaid.* Chicago, Ill: American Medical Association; 1989.

6. Nutter DO. Medical indigency and the public health care crisis: the need for a definitive solution. *N Engl J Med.* 1987;316:1155-1158.

7. American Academy of Pediatrics. *Solutions: An Overview of the Academy's Three-Part Access to Care Campaign.* Elk Grove Village, Ill: American Academy of Pediatrics; 1990.

8. Bunker JP, Gomby DS, Kelvier BH, eds. *Pathways to Health: The Role of Social Factors.* Menlo Park, Calif: The Henry J. Kaiser Family Foundation; 1989.

9. Davis K, Rowland D. Uninsured and underserved: inequities in health care in the United States. *Milbank Q.* 1983;61:149-176.

10. Dutton DB. Social class, health, and illness. In: Aiken LH, Mechanic D, eds. *Applications of Social Science to Clinical Medicine and Health Policy.* New Brunswick, NJ: Rutgers University; 1986:31-62.

11. Wilensky GR. Filling the gaps in health insurance: impact on competition. *Health Aff.* Summer 1988:133-149.

12. Trevino FM, Moyer ME, Valdez B, Stroup-Benham CA. Health insurance coverage and utilization of health services by Mexican Americans, mainland Puerto Ricans, and Cuban Americans. *JAMA.* 1991;265:233-237.

13. Kitzhaber J. Uncompensated care: the threat and the challenge. *West J Med.* 1988;148:711-716.

14. Braverman P, Oliva G, Miller MG, Reiter R, Egerter S. Adverse outcomes and lack of health insurance among newborns in an eight-county area of California, 1982 to 1986. *N Engl J Med.* 1989;321:508-513.

15. Hadley J, Steinberg EP, Feder J. Comparison of uninsured and privately insured hospital patients: condition on admission, resource use, and outcome. *JAMA.* 1991;265:374-379.

16. Kurtzke JF. The current neurologic burden of illness and injury in the United States. *Neurology.* 1982;32:1207-1214.

17. Kurtzke, JF, Bennett DR, Berg BO, Beringer GB, Goldstein M, Yates TS Jr. On national needs for neurologists. *Neurology.* 1986;36:383-388.

18. Leehey M, Gilden D. Neurologic disorders associated with the HIV and HTLV-I viruses. *Cur Neurol.* 1990;10:1-63.

19. Shern D, Dilts SL. The concentration of severely disturbed CMI in a core urban population. *Admin Mental Health.* 1987;15:18-28.

20. Gage LS, Andrulis DP. Our nation's great public hospitals. *JAMA.* 1987;257:1942-1943.

21. Friedman E. Problems plaguing public hospitals: uninsured patient transfers, tight funds, mismanagement and misperception. *JAMA.* 1987;257:1850-1857.

22. Friedman E. Public hospitals often face unmet capital needs, underfunding, and uncompensated patient-care costs. *JAMA.* 1987;257:1698-1701.

23. Bindman AB, Keane D, Lurie N. A public hospital closes: impact on patients' access to care and health status. *JAMA.* 1990;264:2899-2904.

24. Ansell DA, Schiff RL. Patient dumping: status, implications, and policy recommendations. *JAMA.* 1987;257:1500-1501.

25. *A Call for Action: Final Report.* Washington, DC: The Pepper Commission, US Bipartisan Commission on Comprehensive Health Care; 1990.

26. *The Health Care Crisis: A Report to the American People.* Washington, DC: Senate Committee on Labor and Human Resources; 1990.

27. American Medical Association. *Health Access America: The AMA Proposal to Improve Access to Affordable, Quality Health Care.* Chicago, Ill. American Medical Association; 1990.

28. Himmelstein DU, Woolhandler S, the Writing Committee. A national health program for the United States: a physicians' proposal. *N Engl J Med.* 1989;320:120-128.

29. Beauchamp DE, Rouse RL. Universal New York health care: a single-payer strategy linking cost control and universal access. *N Engl J Med.* 1990;323:640-644.

30. Lundberg GD, Bodine L. Fifty hours for the poor. *JAMA.* 1989;262:3045.

31. Mayster V, Waitzkin H, Hubbel A, Rucker L. Local advocacy for the medically indigent: strategies and accomplishments in one county. *JAMA.* 1990;263:262-268.

32. Levit KR, Freeland MS. National medical care spending. *Health Aff.* Winter 1988:124-136.

33. Thorpe KE, Siegel JE, Dailey T. Including the poor: the fiscal impacts of Medicaid expansion. *JAMA.* 1989;261:1003-1007.

34. Blendon RJ. The public's view of the future of health care. *JAMA.* 1988;259:3587-3593.

35. Gabel J, Cohen H, Fink S. Americans' views on health care: foolish inconsistencies? *Health Aff.* Spring 1989:103-118.

36. American Society of Internal Medicine. *Ending Separate and Unequal Health Care.* Washington, DC: American Society of Internal Medicine; 1990.

37. Ginsburg JA, Prout DM. Access to health care: position paper of the American College of Physicians. *Ann Intern Med.* 1990;112:641-661.

38. Earnest MP. Access to health care in the United States: barriers for neurologic patients, challenges for neurologic physicians. *Neurology.* 1990;40:1815-1819.

Access to Neurological Care for Minorities

Edgar J. Kenton, MD

• Minority groups comprise a major segment of the estimated more than 34 million Americans without insurance coverage and also the underinsured. Neurologic disease and neurologic complications of the major causes of morbidity and mortality affect minorities protracted by limited access to health care. Hypertension, a major cause of stroke in the black population, is just one example of the impact of accessibility to intervention in central nervous system disease. Health statistics note the persisting gap between minority groups and the nation's norms for life expectancy. Aging America and particularly black elderly women, combined with the lagging infant mortality among minority groups, demonstrate limited access issues beyond economics, reflecting inner city mores, cultural barriers, and communication delay limiting contact with the practicing neurologist. Awareness of such access limitations to neurological care for minorities demands the attention of the practicing neurologist and the neurological societies.

(*Arch Neurol.* 1991;48:480-483)

Many reports in recent medical and lay literature cite increasingly limited access to our health care system by minority populations. The American College of Physicians, the nation's largest medical specialty society, published a position paper in 1990 calling for a nationwide program to improve access to health care for all Americans.[1] They cited the growing number of Americans without access to health care. It is well documented that access to health care is dependent on one's socioeconomic level and also minorities comprise the majority of the lower socioeconomic scale.[2-4] It follows that limited access to health care affects many minority groups seeking care. Minorities comprise a large component of the estimated 34 to 37 million Americans under age 65 who have no health care insurance.[5] Furthermore, life expectancy among many minority groups has declined in recent years. Mortality rates among the poor and disadvantaged are higher for most causes of death as are prevalence rates of major disabilities including heart disease, cancer, and stroke.[6,7]

Practicing neurologists can attest that complications of heart disease, cancer, and stroke damage the central nervous system. Early intervention can prevent or reduce the severity of those disorders; limited access to medical attention probably accentuates severity. To disadvantaged minorities, neurologic symptoms and signs as well as the discipline itself are enigmas. They may refuse a lumbar puncture for fear of paralysis or fear of spreading the malady, or equate multiple sclerosis with muscular dystrophy or defer a computed tomographic scan or magnetic resonance imaging of the brain for fear of brain injury. Others fail to initiate or maintain medication due to cost.

The incidence of stroke has declined 60% over the past three decades, yet such cannot be stated at a similar rate in minorities.[8] There has been little impact on mortality during the initial 3 days following stroke onset and only a slight improvement in the 30-day mortality rate.[9] Studies have been reported by the National Cancer Institute, the National Minority Health Association Inc, the National Medical Association, and the Urban League, citing the relation of limited access for health care among minorities.[10-13] Hypertension, heart disease, and atherosclerosis are the major factors influencing stroke and are clearly related to access issues. Illustrating the gravity of the current situation, Charles Francis, MD, Director of Medicine, Harlem Hospital, New York, NY, reported on the crises of compliance with antihypertensive medication in the inner city[14] and indicated that hypertension control rates among Harlem patients have fallen from more than 80% to only 50% over the past several years.

Statistics, however, suggest neurologic complications of the leading mortality causes affecting minorities may, indeed, be remedial as attempts are being made by many medical organizations to improve access to health care. The National Center for Health Statistics revealed the average life expectancy in 1988 that for blacks was 69.2 years and for whites, 75.6 years.[15] From 1984 through 1988, the gap between life expectancies for whites and blacks increased from 5.6 years to 6.4 years. However, the year 1989 showed a distinct improvement in life expectancy for the population as a whole over 1988 and in blacks' life expectancy, despite a 32% increase in deaths from human immunodeficiency virus infection and an increase in homicides in the United States. Death rates for cerebrovascular diseases, heart disease, and atherosclerosis were less in 1989 than in 1988; heart disease, stroke, and cancer all showed a decline in mortality compared with those in the previous year. Statistics suggest neurologic complications of such major mortality and morbidity issues, contributors to significant components of the nation's health care costs, demand our attention in removing existing barriers of access to neurological care for minorities.

While the uninsured and the underinsured face socioeconomic barriers inhib-

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iting access to neurological care, there are other minority-based issues that restrict access. As discussed by the several articles in the recent *JAMA* issue on Hispanic health in the United States, there is high minority density in the inner cities where few private doctors and clinics are available and primary health care is provided by overcrowded emergency rooms and public clinics.[16] Those initial lines of medical defense usually do not address the many subtleties of neurologic diagnoses, nor do they provide continuity of care often required in neurologic management, for example, continuing treatment of epilepsy. Generations of minorities distrust such facilities, often remembering the bad experiences of their ancestors; and tradition dies hard.

In addition, many minority senior citizens supported by Medicare and adequate supplementary insurance could afford a private doctor. But often they are admitted from emergency rooms to the teaching services as unassigned patients to be followed thereafter by residents in the outpatient clinics and not as private patients. Thus, they have limited access to more experienced physicians, are exposed to the resident rotation system, and are relegated to a system usually established for the underinsured. Also, how many minority patients have the resources required to secure disability benefits for chronic neurologic impairment from a complex, uncaring, and bureaucratic social services system? They often need legal assistance. Many minority stroke patients with diagnosis related group–limited hospital stay would rather return to the supportive familiarity of the home and family, but cannot because of working spouses or children. Indeed, many minority individuals with primary neurologic illness such as transient ischemic attacks, "mini strokes," multiple sclerosis, disabling peripheral neuropathies, and spondylitic spastic paraparesis never see a neurologist, preferring the continuity of the family physician over the impersonal public clinic or hospital.

To limit access discussions to economic issues and insurance coverage, therefore, avoids historically inculcated and culturally ingrained ingredients that impair utilization of neurologic services. Minorities, regardless of economics, because of their limited contact with physicians of their own background and because of the low rate of preventive physical examinations, such as recommended by the US Preventive Services Task Force, continue to lag behind the nation's norms in access to all health care, including neurologic care.[17] To the extent that acculturation succeeds through education, job opportunities, social and community action programs, and physician participation will access to health care proceed.

The Medicare/Medicaid programs, created in the mid-1960s, produced significant improvement in the health status of minorities. However, those same populations continue to lag behind the white population not only in infant mortality but also in life expectancy of its senior citizens affected by stroke, Parkinson's disease, and dementia.[18,19] *JAMA*, in its issue focusing on minority health, highlighted a 1986 survey on the utilization of health services. That survey demonstrated significant lack of access to health care among black compared with white Americans experienced at all socioeconomic levels. Also, blacks compared with whites were less likely to be satisfied with the quality of physician care and hospital care, and they were more likely to believe length of stay too short.[20-22]

Hypertension, a leading cause of stroke in minorities, seriously impacts on neurologic care. Numerous studies[23-25] reveal that approximately 28% of adult blacks suffer from hypertension compared with about 17% of adult whites and that blacks develop hypertension at a younger age than do whites. Advanced hypertension is five times more common in blacks. Stroke mortality in blacks is 65% higher than that in whites. Black persons with hypertension probably are more susceptible than are hypertensive whites to the neurologic complications of the disease. Yet, according to the *JAMA* articles, whites and blacks respond similarly to antihypertensive therapy, achieving control at about the same numbers.[26] Yet, minority populations do not receive antihypertensive therapy to the same degree as the white population because of access-limiting costs of drugs, continuity of care, early intervention, and education of drug effects. The implications of such limited access to antihypertensive regimens can be seen in such reports by Francis[14] and others[27-30] revealing deteriorated health care for minorities and contributing to end-stage disease.

Other studies have shown that the delay from onset of symptoms for stroke to arrival at the hospital[31] was markedly prolonged for minorities compared with predominantly white populations.[13] The same is true for the latency period from arrival at the hospital to neurologic consultation for minorities, if such consultation is obtained at all.

The "graying" of America is one of the most significant demographic barriers to neurologic care access. Current national population projections indicate that the number in all age categories of 60 years will be considerably larger at the end of this century and will continue to grow for the first three decades of the 21st century. The black elderly are the most economically disadvantaged of any of the minority groups. The black elderly are more likely to be sick and disabled with higher rates of hypertension, cerebrovascular disease, cardiogenic stroke, spondylitic paraparesis, peripheral polyneuropathy, and dementia. Elderly black women are revealed by studies to be the most apt to be living alone, relying on increasingly shrinking access to and availability of our nation's home health care providers.[32]

Recognizing these factors of minority-based health care that contribute to neurologic complications, what is the role of the neurologist in easing access to neurological care? Minorities experience complex health disadvantages related to poverty, disinformation, and racial bias, limiting access to quality health care. However, neurologists first and foremost must be aware of these issues. If we wish to implement the plan proposed by the National Advisory Neurological Disorders and Stroke Council of the National Institute of Neurologic Diseases and Stroke for the "decade of the brain," the issues of access to health care become fundamental for enabling such efforts.[33] Louis Sullivan, MD, Secretary of Health and Human Services, stated that what we do now in areas of prevention will pay off well into the 21st century and that our health, its maintenance, and prevention of disease have become a high priority in the black community.[34]

Matthew Menken, in his editorial in the November issue of the ARCHIVES, concerning the practice of neurology, commented that "As an educational tool the anecdotal method assumes that the practicing physician who is roughly right is preferable to one who is precisely wrong."[35] The wealth of anecdotal experience of practicing neurologists in both the public and private sectors who deal with minority health care indicates that access to neurological care is an important health care issue. Minority patients with stroke, epilepsy, cerebral palsy, dementia, developmental disability, head trauma, and neurological complications of acquired immunodeficiency syndrome need neurological consultations and may need computed tomographic scans or magnetic resonance imaging and then continuing, long-term management. The personal experience of the author and other neurologists[36] indicates that minorities have difficulty obtaining neurologic care. Precise data on the extent of the problem for neurological patients are not available. However, the national problem for minority patients overall is well documented and the problem demands corrective action. Our specialty organizations must mobilize the support and the participation of neurologists in practice to address the chief complaints of the minority community in their quest for access, ie, how to obtain quality neurologic care. The symptoms and signs of access malady must be addressed, ie, problems that minority groups have communicating with providers of neurologic care, plus limited education especially about health, impeding disease detection and prevention, and culturally based lack of motivation to seek help. Many community resources should be utilized to help solve the problem including minority churches, social organizations, and political groups. Practicing neurologists and our specialty societies can develop studies such as conducted by the Robert Wood Johnson Foundation[5] and the Massachusetts Institute of Technology, Cambridge, Mass,[37] and can stimulate activities by private foundations in their community.[38,39] The American Academy of Neurology has established a task force on access to neurologic care.[35] We, as neurologists, must heed the call of the minority community and provide the availability of neurologic care.

Blacks constitute 12% of the population, 4% of doctors under age 40, and only 2.5% of neurology residents in the 1980s.[40] What can and should the neurologic societies do about such disturbing numbers? Programs should be developed in coordination with the task force on access to neurological care, educating its members in such issues. Programs can be provided addressing neurological problems of minorities for presentation to the minority communities in detection and early intervention strategies. High school student programs in minority communities dealing with neurological issues can be highly effective in recruiting medical school applicants. Neurological societies can also encourage minority medical student applicants for currently available student training grants in neurological research. What can individual neurologists do in addition to becoming more aware of this enormously complex issue? In addition to participation in such proposed programs and encouraging such by the various neurological societies, the neurologist must pursue legislation at the federal, state, and local levels addressing these issues. They must educate their colleagues, students, residents, and patients in limiting unessential studies and hospitalizations, becoming allies of third-party payers. They must establish and participate in medical ethics committees for hospital staffs, guiding the appropriate health care and peer review of death and dying for the terminally neurologic patient.

As neurologists we must study the demographics for minority neurology in the United States. Such demographics have yet to be established. While various studies of specific neurologic disorders accumulated in the literature might note the incidence and prevalence of a particular disease in a minority group, usually stated as nonwhite, few indicate specific minority ratios. The changing demographics of the population into the 1990s and the 21st century requires neuro-epidemiologic studies of our shifting black, Hispanic, Asian-American, and Native American populations. One can extrapolate from the Kurtzke[41] data on the neurologic burden of illness and injury in the United States an estimate of individuals with neurologic disorders among the approximated millions of uninsured and underinsured Americans.[36] However, the paucity of minority risk factor data for stroke can be seen in the otherwise comprehensive special report of the World Health Organization task force on stroke and other cerebrovascular disorders published in 1989.[42] Two studies supported by the National Institute of Neurologic Diseases and Stroke are presently addressing the disparity of stroke incidence and mortality between black and white Americans.[43] Studies such as these at Columbia University and the University of Maryland are examples of the need to pursue minority neurologic demographics. A poster presentation on race and incidence of hemorrhagic stroke presented at the stroke meetings in San Francisco is encouraging in this regard.[44]

Finally, the behavior of many office-based neurologists toward Medicaid patients, Medicare assignment, and the many mettlesome problems associated with caring for such patients need to be addressed. Bureaucratic enforced payment fees and burdensome accompanying paperwork are relegating such patients to second-class or lower strata in access to high-level health care. The ever-increasing overhead of the neurologist in office practice limits the entrance of such patients into such quality care assumed by the private-pay patients. Indeed, such rationing of health care inherent in any second-party– and third-party–subsidized delivery system since its inception, is now deeply embedded in various proposals to curtail rising health care costs further challenging the economics and ethics of the office- and hospital-based neurologist. Hence, the neurologist must join the minority community and its leaders in providing incentives to ease such patients in the quality delivery of health care. If various tax and business incentives, long established for businesses and corporations, can be directed toward such access barriers created by Medicaid and Medicare assignments, the neurologist will be aided in behavior modification toward such patients. The skills of the neurologists can be bartered for items of need to exercise such skills just as small businesses are taking such an approach in such recessionary times. The time has come for the community and the health care provider to establish innovative financing strategies to maintain its citizens at the first-class attitudes of both the provider and the recipient.

As Secretary Louis Sullivan, MD, indicated in his keynote address to a satellite meeting of the 1991 International Conference on Stroke, the costs of stroke is a $25 billion health problem and stroke is a discriminating disease disproportionately affecting women and blacks. Secretary Sullivan highlighted access to medical care, contingent on personal responsibility for disease prevention, containment of health care costs, a public health system for the poor, a reexamination of the private insurance system, and providing outcome studies of effectiveness of treatment strategies.[45] In all such areas, the neurologist and neurological societies need participate.

References

1. American College of Physicians Position Paper. Access to health care. *Ann Intern Med.* 1990;112:641-661.

2. Kleinman JC, Gold M, Makuc D. Use of ambulatory medical care by the poor: another look at equity. *Med Care.* 1981;19:1011-1028.

3. Aday LA, Fleming GV, Anderson R. *Access to Medical Care in the US: Who Has It, Who Doesn't.* Chicago, Ill: Pluribus Press; 1984.

4. Bunker JP, Gomby DS, Kehrer BH. *Pathways to Health: The Role of Social Factors.* Menlo Park, Calif: The Henry J. Kaiser Family Foundation; 1989.

5. Robert Wood Johnson Foundation Special Report. *Access to Health Care in the United States: Results of a 1986 Survey.* Princeton, NJ: Robert Wood Johnson Foundation; 1987.

6. National Center for Health Statistics. *Vital Statistics of the United States, 1979: Mortality.* Washington, DC: Public Health Service; 1984;2, pt A. US Dept of Health and Human Services publication (PHS) 84-1101.

7. Report of the Secretary's Task Force on Black and Minority Health. Washington, DC: US Dept of

Health and Human Services; August 1985.

8. Whisnant JP. The role of the neurologist in the decline of stroke. *Ann Neurol.* 1983;14:1-7.

9. Garraway WM, Whisnant JP, Drury I. The changing pattern of survival following stroke. *Stroke.* 1983;14:699-702.

10. *Proceedings of the National Black Leadership Initiative on Cancer-Regional Meetings.* Bethesda, Md: National Cancer Institute; 1988.

11. Foard F. *Minority Health News.* Harrisburg, Pa: National Minority Health Association, Inc; 1990.

12. Jones B. Disproportionate health risk in minorities: does medical education need to change? *J Natl Med Assoc.* 1990;82:395-396.

13. Leffall LD. *Health Status of Black Americans: The State of Stroke America, 1990.* Washington, DC: Urban League; 1990.

14. Francis C. The crisis of compliance with antihypertensive medications in the inner city: causes and hope. In: *Medical Intelligence Alert.* Patterson, NY: Caduceus Medical Publishers Inc; 1990.

15. National Center for Health Statistics. Advance report of final mortality statistics. *Month Vital Stat Rep.* 1989;38(suppl 5):1-47.

16. Council Report. Hispanic health in the United States. *JAMA.* 1991;265:248-252.

17. US Preventive Services Task Force. *Guide to Clinical Preventive Services.* Baltimore, Md: Williams & Wilkins; 1989.

18. *Health of America's Children.* Washington, DC: Children's Defense Fund; 1989.

19. Edelman, M. Black children in America. In: *The State of Black America.* Washington, DC: Urban League; 1989:63-76.

20. Blendon RJ, Aiken LH, Freeman HE, Corey CR. Access to medical care for black and white Americans: a matter of continuing concern. *JAMA.* 1989;261:278-281.

21. Freeman HE, Blendon RJ, Aiken LH, et al. Americans report their access to care. *Health Aff (Millwood).* 1987;6:6-18.

22. *Report of the Secretary's Task Force on Black and Minority Health.* Bethesda, Md: Dept of Health and Human Services, August 1985.

23. Caplan LR, Gorelick PB, Hier DB. Race, sex, and occlusive cerebrovascular disease: a review. *Stroke.* 1986;17:648-655.

24. Berkson DM, Brown MC, Stanton H. Changing trends in hypertension detection and control: the Chicago experience. *Am J Public Health.* 1980;70:389-393.

25. Hypertension Detection and Follow-up Program Cooperative Group. Blood pressure studies in 14 communities. *JAMA.* 1977;237:2385-2391.

26. Kirn TF. Research seeks to reduce toll of hypertension, other cardiovascular diseases in black population. *JAMA.* 1989;261:195.

27. McCord C, Freeman HP. Excess mortality in Harlem. *N Engl J Med.* 1990;322:173-177.

28. Ginzberg E. Access to health care for Hispanics. *JAMA.* 1991;265:238-241.

29. Svensson CK. Representation of American blacks in clinical trials of new drugs. *JAMA.* 1989;261:263-265.

30. Beardsley EH. *A History of Neglect: Health Care for Blacks and Mill Workers in the Twentieth Century South.* Knoxville, Tenn: University of Tennessee Press; 1987.

31. Alberts MJ, Bertels C, Dawson DV. An analysis of time of presentation after stroke. *JAMA.* 1990;263:65-68.

32. Ramashala MF. The state of the black elderly in Philadelphia. In: *The State of Black Philadelphia.* Philadelphia, Pa: Urban League; 1987.

33. The National Advisory Neurological Disorders and Stroke Council. *Implementation Plan Decade of the Brain.* Bethesda, Md: National Institute of Neurologic Diseases and Stroke; 1990.

34. Sullivan L. Report of National Black Leadership Initiative on Cancer. Presentation to the National Cancer Advisory Board; December 1988.

35. Menken M. The practice of neurology. *Arch Neurol.* 1990;47:1173.

36. Earnest MP. Access to health care in the United States: barriers for neurologic patients, challenges for neurologic physicians. *Neurology.* 1990;40:1815-1819.

37. *Education That Works: An Action Plan for the Education of Minorities: Quality Education for the Minorities Project.* Cambridge, Mass: Massachusetts Institute of Technology; 1990.

38. Olson CM. Health educators turn to black community's leaders, organizations, other strengths. *JAMA.* 1989;261:194-195.

39. Menken M. Caring for the uninsured and underinsured. *Arch Neurol.* 1991;48:23.

40. *Health Status of the Disadvantaged: Chartbook 1990.* Washington, DC: Dept of Health and Human Services; 1990.

41. Kurtzke JF. The current neurologic burden of illness and injury in the United States. *Neurology.* 1982;32:1207-1214.

42. World Health Organization. *Report of the WHO Task Force on Stroke and Other Cerebral Vascular Disorders: Stroke—1989.* Geneva, Switzerland: World Health Organization; 1989.

43. *Stroke 1990 Research Program NINDS.* Bethesda, Md: Dept of Health and Human Services 1990.

44. Broderick JP, Brott TG, Miller R, Huster G. Race and incidence of hemorrhagic stroke. *Stroke.* 1991;22:126. Abstract.

45. Sullivan L. Socio-economic impact and racial considerations. Presented at the Satellite Meeting of the Sixteenth International Conference on Stroke; February 21, 1991; San Francisco, Calif.

Original Contributions

Clinical Evaluation of Stenosis of the Carotid Bifurcation With Magnetic Resonance Angiographic Techniques

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• We evaluated the images of 60 carotid artery bifurcations in 31 patients suspected to have carotid artery disease who underwent invasive carotid angiography and combined two-dimensional, phase-sensitive and a gradient-echo magnetic resonance angiography. The phase scans consisted of seven serial projections that were obtained at 20° intervals (11.0 minutes) around the carotid bifurcation; the gradient-echo (GRASS) scans were composed of 11 axial images (2.4 minutes) acquired through the bifurcation. The two magnetic resonance angiographic techniques yielded complementary pieces of information and were used together to compare magnetic resonance angiography with invasive angiography. Comparison of magnetic resonance and invasive angiograms of the 60 carotid arteries shows that the sensitivity (86%) and specificity (92%) of the magnetic resonance angiographic techniques we used to diagnose clinically significant carotid stenosis approach but do not reach those of invasive angiography.

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Stroke is the third leading cause of mortality in the United States and affects 1.7 million people at any time.[1,2] Up to 15% to 20% of strokes may be related to potentially remediable atherosclerotic changes in carotid arteries.[3] Carotid endarterectomy is generally recommended for symptomatic patients with relevant severe stenosis in their extracranial carotid arteries, at least pending the completion of a number of ongoing trials of this surgical procedure.[4] Platelet antiaggregants (eg, aspirin) are usually employed in patients with less severe carotid artery disease or in those who are at high surgical risk.[5-8]

Patients suspected to have clinically significant carotid atherosclerotic plaques undergo imaging with a variety of techniques. Ultrasound is the most commonly used noninvasive method. Most laboratories employ Duplex scanning, which provides B-mode images, complemented by Doppler flow signals, because the accuracy of B-mode imaging alone decreases as the severity of the stenosis of the carotid artery increases.[9,10] Color-coded Doppler imaging allows simultaneous imaging of blood flow and soft tissue and may prove to be advantageous in the depiction of tortuous vessels, postendarterectomy states, and preocclusive stenosis.[11,12]

Magnetic resonance (MR) angiography is another noninvasive technique that can produce two-dimensional, as well as three-dimensional, images of the carotid arteries. A variety of techniques, which take advantage of either the longitudinal or transverse (phase) magnetization of protons in the field of interest,[13-15] can be utilized to produce images of blood vessels. The purpose of our study was to evaluate the sensitivity and specificity of two MR angiographic techniques compared with invasive angiography in the identification of clinically significant stenosis of the carotid artery near the bifurcation. An older, well-established, phase-sensitive MR angiographic technique was used to produce two-dimensional images similar to those produced by invasive angiography, both to identify stenosis and to localize the carotid bifurcation so that axial gradient-echo images can be obtained through the carotid bifurcation in cross-section. The axial gradient-echo images were acquired to estimate the percentage of stenosis, as they usually disclose more accurate contour information than do the phase images.

PATIENTS AND METHODS

Forty-one patients with suspected carotid artery disease who had undergone invasive carotid angiography (intravenous [IV] digital substraction angiography [DSA], intra-arterial DSA, or conventional invasive angiography) within approximately 24 hours were entered into this open-ended study. Patients were excluded from this study if they were claustrophobic, had a cerebral aneurysm that had been clipped, had a pacemaker, or had recently undergone carotid surgery. After being fully informed about the nature of MR angiography, informed consent was obtained from all the patients who participated in the study.

Of the patients recruited, two were excluded from the study because a scan could not be successfully completed; another two were excluded because some of the images were inadvertently omitted; and a final two were excluded because of mechanical or soft-

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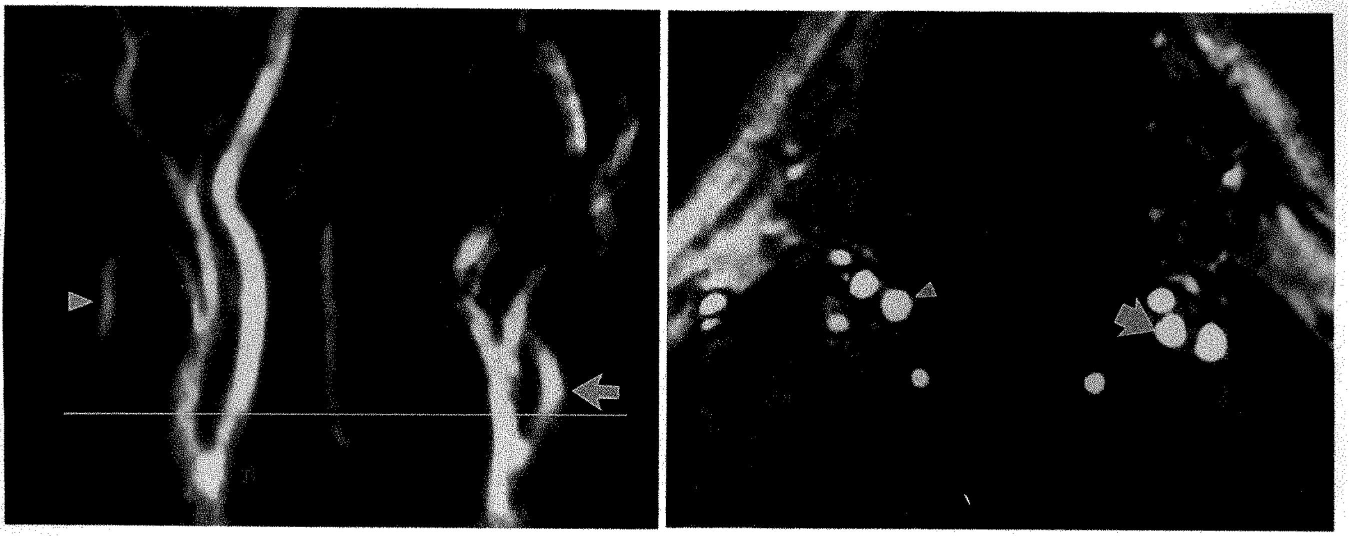

Fig 1.—Images of normal carotid arteries. Left, Magnetic resonance phase-projection angiogram through both carotid artery bifurcations. The right internal carotid artery (ICA) does not overlap the right external carotid artery (ECA) as it does on the left (arrow). The right ICA is medial to the corresponding ECA, while the reverse is true on the left. The right ECA can be differentiated from the ICA because of its branches (arrowhead). Right, Axial gradient-recalled acquisition in the steady state image through the carotid bifurcation (acquired through a plane represented by the horizontal line in Fig 1, left). The right ICA (arrowhead) is posteromedial to the corresponding ECA because of its unusual medial position, while the contralateral left ICA (arrow) is almost directly posterior to the ECA (usual anatomic situation). Both ICAs are slightly larger than the ECAs.

Table 1.—Comparison of Magnetic Resonance (MR) Angiographic and Invasive Angiographic Findings on Degree of Carotid Stenosis

	Invasive Angiogram*							
MR Angiogram	**Normal**	**Minor**	**Moderate**	**Severe**	**Severe/High-Grade†**	**High-Grade**	**Occluded**	**Total**
Normal	7	6	1	0	0	0	0	**14**
Minor	2	7	1	2	0	1	0	**13**
Moderate	2	2	6	0	0	0	0	**10**
Severe	0	1	2	1	0	2	0	**6**
Severe/high-grade†	0	0	0	1	0	0	0	**1**
High-grade	0	0	0	4	0	10	0	**14**
Occluded	1	0	0	0	0	0	1	**2**
Total	**12**	**16**	**10**	**8**	**0**	**13**	**1**	**60**

*Minor indicates 1% to 15%; moderate, 16% to 49%; severe, 50% to 79%; high-grade, 80% to 99%; and occluded, 100%.

†The combined category means that the "gold standard" committee judged the two grades of stenosis to be equally probable.

ware difficulties associated with the scanner.

Both a phase-sensitive, projection angiographic technique and a gradient-echo technique that produces transaxial images were used with a 1.5-T system with linear gradient coils.[15,16] A localizing scan was obtained to ensure that the carotid bifurcations were in the center of the field (2.4 minutes). Seven separate projection images were then obtained at 20° intervals (11.0 minutes; repetition time, 33 msec; echo time, 17 msec; 22 signals averaged; field of view, 16 cm; 256 × 128 matrix).

The projection image that best showed the location of the carotid bifurcation was then used to obtain a sequence of 11 axial images through the carotid bifurcation and proximal internal carotid arteries (Fig 1). The technique of gradient-recalled acquisition in the steady state (GRASS) (2.4 minutes; flip angle, 70°; repetition time 55 milliseconds; echo time, 17 milliseconds; 2 signals averaged; field of view, 16 cm; section thickness, 5 mm; 256 × 128 matrix) was used to obtain the axial images from which the percentage of narrowing was estimated.

Each combined MR angiogram and the corresponding invasive angiogram was interpreted by a panel of physicians, which consisted of a vascular surgeon (K.O.), a neurologist (J.H.), and three neuroradiologists (L.M.K., A.M., J.V.M.). All readings were performed by a minimum of two members of the panel, at least one of whom was a neuroradiologist. The MR images were always reviewed before the invasive angiograms. No history or clinical findings were provided beyond knowledge that the patient was being evaluated for suspected disease of the carotid arteries. The quality of each image was graded to allow separate analysis of those scans that were technically inadequate. The positions of the internal and external carotid arteries were identified, when possible, from the projection images. These images were also used to identify grossly the areas of stenosis. Each carotid artery was evaluated for stenosis relative to the normal segment of the internal carotid artery distal to the stenosis (none; minor, 1% to 15%; moderate, 16% to 49%; severe, 50% to 79%; high-grade, 80% to 99%; or occlusion) based on the axial GRASS images (Fig 1). The axial GRASS images were compared with the phase images, because the former occasionally underestimate the degree of stenosis. A confidence level (seven steps from definite to unlikely) was also assigned to each finding.

Among the 70 carotid arteries examined by the committee, 10 were excluded for one of two reasons: (1) Two carotid arteries were excluded because the invasive angiogram (an IV DSA study) was judged by the "gold standard" committee to be of poor quality. Four other carotid arteries were excluded from the analysis because the MR angiograms were of insufficient quality to be read. (2) Four carotid arteries were excluded because the sum of the committee's confidence in their primary and alternative interpretations of the MR angiograms did not exceed 50%. In these cases, the committee stated that they were having difficulty distinguishing between the internal and external carotid arteries.

The mean age of the 31 patients with carotid arteries analyzed in our study was 69.5 years (range, 48 to 85 years). There were 22 men and nine women. The mean age for the 10 patients enrolled in the study who were later excluded from the analysis was not significantly different (70.2 years); however, these patients were evenly divided between men and women. Ninety percent of the 31 patients underwent intra-arterial invasive angiography, and 10% underwent IV DSA invasive angiography. In all three of the IV DSA studies that were included, the review committee judged the images to be of sufficient quality to permit accurate measurement of carotid stenosis.

Statistical analysis was performed with use of the Statistical Analysis System.[17] Pearson correlation coefficients and Kendall's τ were used as measures of association. Fisher's Exact Test and χ^2 analysis were used for pairwise comparisons of categorical data. Sensitivity and specificity were calculated with standard methods.[18]

RESULTS

Among the 70 carotid bifurcations examined, 60 met our criteria for analysis: the images were of adequate quality and the review committee had reasonable confidence in their readings. All subsequent analyses presented will refer to these 60 carotid arteries.

In 53% of the carotid arteries, the stenosis ratings based on the MR angiograms were an exact match with the results of the corresponding invasive angiograms. Of the remaining pairs, 33% were off by one step or less and 13% by two or more steps (Table 1). Magnetic resonance angiograms overestimated the size of the lumen in 15 of the cases and underestimated it in 13 cases. The correlation between gradings of stenosis based on MR and invasive angiography was .473 for the right side by Kendall's τ correlation coefficient compared with .817 for the left side. These results indicate a highly significant association between the findings of the two tests on both sides.

The clinical significance of the relatively low rate of exact matches (53%) is best evaluated by a comparison of MR angiography with the gold standard—invasive angiography—with use of a 2×2 table to determine the operating characteristics of the MR techniques (Fig 2). Normal findings, as well as minor and moderate stenoses, were regarded as negative (clinically insignificant) results, as the corresponding therapy would probably be medical. In contrast, findings of severe or high-grade stenosis were regarded as positive (clinically significant), as the patients would be potential surgical candidates. For analyses of sensitivity and specificity, occlusion was considered a nonsurgical result. With the use of these definitions, there were 21 carotid arteries with clinically significant stenosis, 38 without clinically significant stenosis, and one occlusion based on the invasive angiograms. With invasive angiographic findings as the gold standard, the sensitivity of MR angiography was 86% (18/21) and its specificity was 92% (36/39). Magnetic resonance angiography was considerably more sensitive in identifying stenosis of the left carotid artery compared with the right.

Right Side

		Invasive Angiography		
		Positive	Negative	
MR Angiography	Positive	8	1	Sensitivity=73%
	Negative	3	18	Specificity=95%

Left Side

		Invasive Angiography		
		Positive	Negative	
MR Angiography	Positive	10	2	Sensitivity=100%
	Negative	0	18	Specificity=90%

Both Sides

		Invasive Angiography		
		Positive	Negative	
MR Angiography	Positive	18	3	Sensitivity=86%
	Negative	3	36	Specificity=92%

Fig 2.—Accuracy of magnetic resonance angiography vs invasive angiography. The right and left carotid arteries are analyzed separately (top and middle) and then together (bottom).

Two of the three false-negative MR readings occurred when the readers did not correctly identify the position of the internal carotid artery. In one case, a large external carotid artery was thought to be the internal carotid artery and thus was read as normal (Fig 3). In the second case, the anatomic variation where the internal carotid lies medial to the external carotid artery was not appreciated and the internal carotid ar-

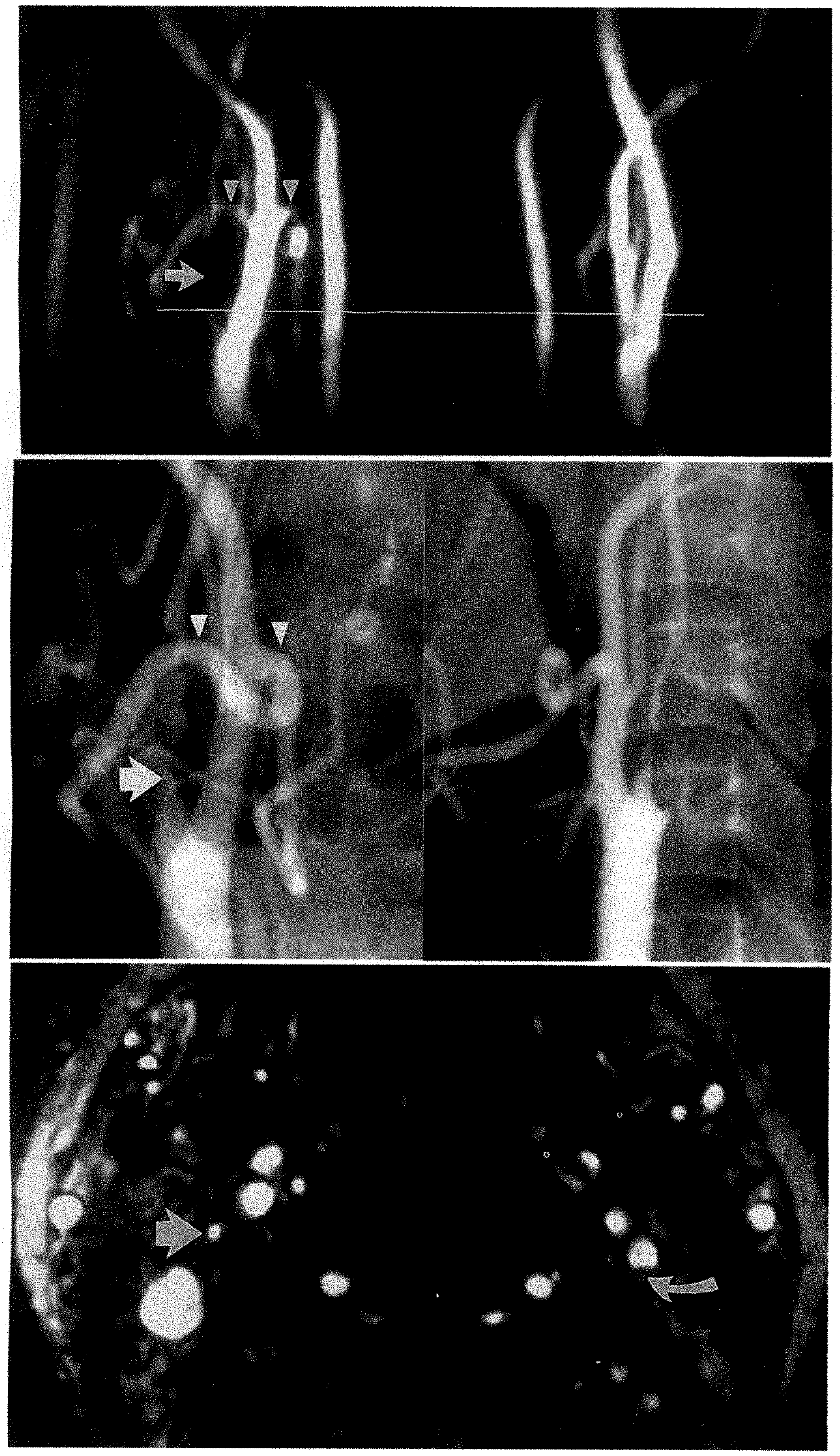

Fig 3.—High-grade stenosis of the right internal carotid artery (ICA). Top, Magnetic resonance phase-projection angiogram shows a prominent artery believed to be a normal right ICA. However, the branches that appear to arise from this vessel (arrowheads) indicate that it is the external carotid artery (ECA). The narrow ICA is lateral to the ECA and shows high-grade stenosis (arrow). Middle left and right, Corresponding anteroposterior (left) and lateral (right) invasive angiograms of the right carotid bifurcation. Note high-grade stenosis of the ICA (arrow). Arrowheads are placed on a branch of the ECA in the left image to correspond to the magnetic resonance phase-projection angiogram (Fig 3, top). Bottom, Axial gradient-recalled acquisition in a steady state images through the neck (acquired through a plane represented by the horizontal line in Fig 3, top). The right ICA shows high-grade stenosis (straight arrow). The left ICA demonstrates minor stenosis due to a small plaque along its posterior wall (curved arrow).

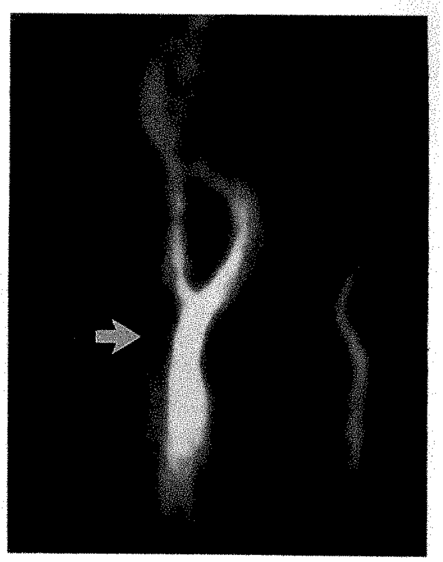

Fig 4.—Medial right internal carotid artery (unusual anatomic position). The lumen of the internal carotid artery was misinterpreted as being normal, because the presence of the superior thyroid artery (arrow) was not appreciated and the lumen size of the external carotid artery was attributed to the internal carotid artery. (Magnetic resonance phase-projection angiogram.)

tery was misjudged to be narrowed (Fig 4). In the third case, the readers underestimated the true stenosis on the MR angiographic images.

The three false-positive readings resulted in cases where the axial GRASS images misrepresented the lumen size of the carotid arteries (Fig 5). In these cases, the lumen appeared to be smaller than it actually was. This distortion might have been suspected by studying the corresponding phase-projection images, which were more similar in appearance to the corresponding invasive angiogram. Four of the six incorrect readings (all three false-negative findings and one false-positive finding) involved the right carotid artery.

The review panel had more confidence in their evaluation of the grade of stenosis when reading the invasive angiograms compared with the MR angiograms. They had a confidence level of 95% or greater (definite or very high) in their readings of 74% of the invasive angiograms vs 28% of the MR angiograms (Table 2).

If the 10 carotid arteries excluded from the analysis had been included, the sensitivity and specificity of MR angiography each would decline slightly. The sensitivity would decline from 86% to 84%; the specificity, from 92% to 87%. The six carotid arteries excluded because of the poor quality of the images included one true-positive, three true-negative, and two false-positive results.

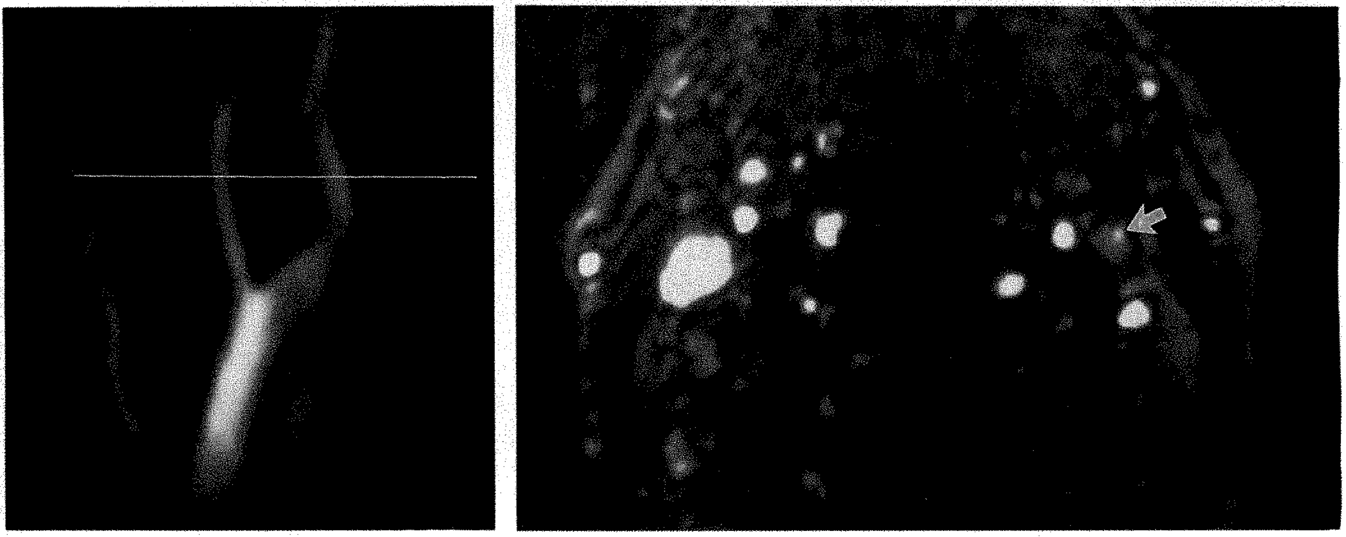

Fig 5.—Minor stenosis of the left internal carotid artery. Left, Phase angiogram appears to be normal. The corresponding invasive angiogram (not shown) disclosed minor stenosis. Right, Axial scan (acquired through a plane represented by the horizontal line in Fig 5, left) shows a small area of high signal intensity (arrow). This was misinterpreted as the residual lumen, so the left internal carotid artery was believed to be severely stenotic. The intermediate signal intensity posteromedial to the high signal intensity, which represents the remainder of the actual lumen, was believed to be a plaque. The right internal carotid artery was judged to have minor stenosis because it was slightly smaller than the corresponding external carotid artery.

Table 2.—Comparison of Degree of Confidence in Readings of Magnetic Resonance (MR) Angiograms vs Invasive Angiograms*

	No. (%)	
Degree of Confidence	MR Angiography	Invasive Angiography
Definite (100%)	...	17 (27)
Very high (95%-99%)	18 (28)	30 (47)
High (76%-94%)	15 (23)	9 (14)
Moderately high (51%-75%)	24 (38)	7 (11)
Moderately low (26%-50%)	6 (9)	1 (2)
Low (6%-25%)	1 (2)	...
Total	**64**	**64**

*This table includes the 60 carotid arteries examined in the analysis and the four carotid arteries excluded because the committee did not have sufficient confidence in their readings. It does not include the six carotid arteries excluded because of poor image quality. Interestingly, the committee's confidence in these six readings did not differ significantly between the invasive and MR angiograms.

The four carotid arteries excluded because of the committee's low confidence in their reading consisted of two true-positive, one false-positive, and one false-negative result.

The 12 remaining carotid arteries excluded were in patients who did not complete the MR imaging procedure as a result of patient or imaging problems. If MR angiography were adopted for clinical practice, however, the four patients (eight carotid arteries) whose imaging procedures were incomplete would have had the missing or inadequate sequences repeated. The two patients (four carotid arteries) who were claustrophobic would have been reassured; if that were inadequate, the patients would have been sedated and the imaging procedure repeated.

COMMENT

Evaluation of an evolving technology is difficult because there are frequently many competing variations, and the newest technique often looks more promising than the older ones. Our study focuses on two well-established MR techniques. Although some might question our reporting on an evaluation of techniques that are no longer on the cutting edge, doing so can be justified for two reasons: (1) It is not clear that just because some of the newer methods produce "prettier" images, they are any more accurate than the older techniques. Until the alternative MR angiographic techniques are compared systematically, it is impossible to conclude which one actually produces the most useful and reliable results. (2) Evaluation of these two methods sets a baseline for the assessment of later techniques. If the results show, as they do in our study, that the operating characteristics of these older techniques come close to those of invasive angiography, they provide additional evidence that MR angiography warrants further, systematic study.

In fact, the results of our study, in which the two older techniques are combined, show that MR angiography can detect clinically significant extracranial carotid artery stenosis without the use of contrast media injection. With invasive angiography as the gold standard, our research shows that MR angiography has good but not perfect sensitivity and specificity.

Our results also indicate that phase (transverse) and longitudinal (gradient-echo) MR angiographic techniques provide complementary pieces of information and thus justify their being evaluated together vs invasive angiography. At least some of the false-positive readings might have been avoided if the gradient-echo images, which underestimated the lumen size, had been compared more carefully with the phase images.

Our study compares the sensitivity and specificity of combining phase-sensitive and gradient-echo MR angiographic techniques with conventional invasive angiography in the identification of clinically significant stenosis of the carotid artery bifurcation. Previously, we had determined that MR angiography does not need to be perfectly sensitive or specific, because a small loss of accuracy would be offset by the lower risk of MR angiography. We estimated, with the use of decision analysis, that carotid MR angiograms can be either 5% less sensitive or 15% less specific than invasive angiograms and still yield the same benefit.[19] Based on these preliminary results, the 86% sensitivity and 92% specificity of MR angiography approach these criteria.

We used invasive angiography as the gold standard for this analysis; it is possible that some apparent MR angiography errors were actually the result of invasive angiography errors. However, analysis with use of only the best MR and invasive angiograms yielded essentially the same results. Similarly, inclusion of the three cases (six carotid arteries) in which IV DSA was used did not lower the operating characteristics of MR angiography, as there were three true-positive and three true-negative results.

Four of the six incorrect readings were of the right carotid artery. Two of the four (two false-negative results) can be attributed to the anatomic variation where the internal carotid artery lies medial to the external carotid artery; this occurs in 17.6% of right carotid arteries and only 5.2% of left carotid arteries.[20] Therefore, it is not surprising that MR angiograms of the right carotid artery were misread more often. However, new three-dimensional, time-of-flight MR angiographic techniques should help overcome this problem by providing a more detailed picture of the carotid bifurcation, whereby the branches of the external carotid artery can be routinely identified.[21-23]

Although our results are promising, it may be difficult for individuals who are inexperienced in the interpretation of MR angiograms to duplicate them. The panel of physicians had been reading normal and abnormal MR angiograms for about 1 year before these images were read for study purposes, and they had become acquainted with many of the pitfalls of MR angiogram interpretation. Furthermore, MR angiograms may be more difficult to read than traditional invasive angiograms, as reflected by the approximately 15 to 20 minutes necessary to read a combined MR angiogram vs roughly 5 minutes for an invasive angiogram.

Several of our findings are consistent with MR angiography being a new technology. In this initial work, the MR angiographic images were more often of lower quality than the invasive angiograms, which could have affected the length of time it took for the committee to read them. Readers' confidence in their gradings of stenosis was consistently lower with MR angiography than with invasive angiography. Both of these differences should decrease as the technology improves and as the readers become even more familiar with it. Consequently, we anticipate that as the field evolves, both the sensitivity and specificity of MR angiography should improve. In fact, some of the techniques presently available elsewhere, individually or in concert, may yield more accurate results than those reported in this study.[22,23] However, past methodologic evaluations of MR studies have shown that strict adherence to sound technologic assessment methods has been the exception rather than the rule.[24,25] Reports of improved results with newer MR techniques should be examined carefully.

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References

1. Robins M, Baum HM. Incidence. *Stroke.* 1981;12(suppl 1; special ed):45-57.
2. Baum HM, Robins M. Survival and prevalence. *Stroke.* 1981;12(suppl 1; special ed):59-68.
3. Mohr JP, Barnett JHM. Classification of ischemic strokes. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. *Stroke: Pathophysiology, Diagnosis, and Management.* New York, NY: Churchill Livingstone Inc; 1986:281-291.
4. Callow AD, Caplan LR, Correll JW, et al. Carotid endarterectomy: what is its current status? *Am J Med.* 1988;85:835-838.
5. Grotta JC. Current medical and surgical therapy for cerebrovascular disease. *N Engl J Med.* 1987;317:1505-1516.
6. Hass WK, Easton JD, Adams HP Jr, et al. A randomized trial comparing ticlopidine hydrochloride with aspirin for the prevention of stroke in high-risk patients. *N Engl J Med.* 1989;321:501-507.
7. Bousser MG, Eschwege E, Haguenau M, et al. 'AICLA' controlled trial of aspirin and dipyridamole in the secondary prevention of athero-thrombotic cerebral ischemia. *Stroke.* 1983;14:5-14.
8. Canadian Cooperative Study Group. A randomized trial of aspirin and sulfinpyrazone in threatened stroke. *N Engl J Med.* 1978;299:53-59.
9. Comerota AJ, Cranley JJ, Katz ML, et al. Real-time B-mode carotid imaging: a three-year multicenter experience. *J Vasc Surg.* 1984;1:84-95.
10. Middleton WD, Foley WD, Lawson TL. Color-flow Doppler imaging of carotid artery abnormalities. *AJR Am J Roentgenol.* 1988;150:419-425.
11. Langlois Y, Roederer GO, Chan A, et al. Evaluating carotid artery disease: the concordance between pulsed Doppler/spectrum analysis and angiography. *Ultrasound Med Biol.* 1983;9:51-63.
12. Merritt CRB. Doppler color flow imaging. *J Clin Ultrasound.* 1987;15:591-597.
13. Wedeen VJ, Meuli RA, Edelman RR, et al. Projective imaging of pulsatile flow with magnetic resonance. *Science.* 1985;230:946-948.
14. Nishimura DG, Macovski A, Pauly JM, Conolly SM. MR angiography by selective invasion recovery. *Magn Reson Med.* 1987;4:113-302.
15. Dumoulin CL, Souza SP, Hart HR. Rapid scan magnetic resonance angiography. *Magn Reson Med.* 1987;5:238-245.
16. Dumoulin CL, Hart HR Jr. Magnetic resonance angiography. *Radiology.* 1986;161:717-720.
17. SAS Institute Inc. *SAS Users Guide: Basics.* Version 5th ed. Cary, NC: SAS Institute Inc; 1985.
18. Ingelfinger JA, Mosteller F, Thibodeau LA, Ware JH. *Biostatistics in Clinical Medicine.* New York, NY: Macmillan Publishing Co Inc; 1983.
19. Tomai LA, Panzer RJ, Phelps CE, Kido DK. Noninvasive carotid artery imaging with magnetic resonance imaging: what is the challenge region for equal efficacy with invasive angiography? *Med Decis Making.* 1988;8:339.
20. Teal JS, Rumbaugh CL, Bergeron RJ, Segall HD. Lateral position of the external carotid artery: a rare anomaly? *Radiology.* 1973;108:77-81.
21. Rossnick S, Dzik S, Starewicz P, et al. Three-dimensional display of blood vessels in magnetic resonance imaging. *Health Care Instrumentation.* 1986;1:201-204.
22. Masaryk TJ, Modic MT, Ruggieri PM, et al. Three-dimensional (volume) gradient echo imaging of the carotid bifurcation: preliminary clinical experience. *Radiology.* 1989;171:801-806.
23. Dumoulin CL, Cline HE, Souza SP, Wagle WA, Walker MF. Three-dimensional time-of-flight magnetic resonance angiography using spin saturation. *Magn Reson Med.* 1989;11:35-46.
24. Panzer R, Kido D, Hindmarsh T. A methodologic assessment of studies comparing magnetic resonance imaging and computed tomography of the brain. *Acta Radiol.* 1986;(suppl 369):269-274.
25. Kent DL, Larson EB. Magnetic resonance imaging of the brain and spine: is clinical efficacy established after the first decade? *Ann Intern Med.* 1988;108:402-424.

Delayed Visual Loss due to Trauma of the Internal Carotid Artery

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• The group of six patients in this study experienced delayed visual loss following head trauma. Visual loss occurred from 1 day to 13 years after the initial injury. All patients suffered indirect trauma to the internal carotid artery resulting in formation of either an aneurysm or pseudoaneurysm or a carotid-cavernous fistula. Review of the radiologic and clinical findings was performed in six patients. The diagnosis was established by computed tomography, magnetic resonance imaging, and angiography. All patients had follow-up clinical evaluation and imaging studies. Treatment by neurosurgical or interventional neuroradiologic procedures resulted in significant visual improvement in five patients. Different pathophysiologic mechanisms could be correlated with the delayed visual loss produced by the two types of lesions. The pathologic changes associated with the aneurysms/pseudoaneurysms included direct compression of optic nerves and/or chiasm and intracranial hematoma. A carotid-cavernous fistula caused delayed visual loss by either hematoma at the orbital apex or compression of the chiasm and/or optic nerves by saccular dilatation of the cavernous sinus. The delayed onset of decreased vision following head trauma should alert the physician to the possibility of a traumatic aneurysm/pseudoaneurysm or a carotid-cavernous fistula. Different neuro-ophthalmologic symptoms can usually be correlated with the pathologic changes demonstrated by neuroimaging procedures.

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Optic nerve damage is a well-recognized complication of closed head trauma.[1-3] In the majority of patients in whom vision can be assessed, visual loss is immediate and nonprogressive. In a significant minority of patients, visual deterioration occurs after an initial stable interval of 12 to 72 hours, at times without an immediate posttraumatic visual deficit. We have observed six patients in whom visual loss occurred weeks to years after an episode of head trauma (Table). The clinical histories of three patients are given in detail. All patients sustained damage to the internal carotid artery. Two different pathophysiologic mechanisms for visual loss were identified. In two patients, visual loss resulted from compressive optic neuropathy due to a carotid-cavernous fistula. In four patients, a traumatic aneurysm or pseudoaneurysm of the carotid artery caused optic nerve compression. In all of the patients with aneurysms or pseudoaneurysms, and in one patient with carotid-cavernous fistula, intervention resulted in prompt restoration of vision to near normal.

REPORT OF CASES

CASE 1.—**Clinical History and Examination.**—A 21-year-old man was in good health until July 1988 when he sustained bilateral basilar skull fractures in an automobile accident. He was unconscious for 3 to 4 hours and awoke with complete loss of vision in the left eye. Vision in the right eye was 20/20. A left third nerve palsy was present; there were also palsies of nerves VII and and V1-3. Intractable keratopathy necessitated a complete left tarsorrhaphy in August 1988. He had had no visual complaints and was able to read small newsprint without difficulty until September 1988, when he noticed progressive visual loss in the right eye. His visual acuity at that time was 20/50 in the right eye, and there was no light perception in the left eye. About 2 weeks after the onset of visual loss, he noted proptosis and redness of the right eye as well as a bruit in the right ear. A right periorbital headache was present. By mid-October 1988, his vision in the right eye had dropped to 20/400.

On January 25, 1989, the patient's visual acuity was 20/400 eccentrically in the right eye and no light perception in the left eye. He correctly identified only six of 14 color plates. The right pupil reacted sluggishly and the left pupil, which could be seen only in its medial aspect at the edge of the tarsorrhaphy, appeared to be fixed and dilated. The visual field of the right eye showed central and inferior arcuate loss (Fig 1). Mild palsies were present in the following cranial nerves: right VI, right IV, left V1-3, and left VII, with aberrant regeneration of left VII. Motility of the left eye could not be fully evaluated because of the tarsorrhaphy, but there was mildly decreased adduction. The right optic disc and retina were normal, except for mild dilation and tortuosity of the veins. The left optic disc was pale with a slightly decreased caliber of the retinal vessels. A high-pitched, low-intensity bruit was heard best over the right orbit, retromastoid area, and posterior occiput. The exophthalmometry reading was 22 mm in the right eye, and it was not obtainable in the left eye because of the tarsorrhaphy. The palpebral and bulbar conjunctiva and the episclera contained typical "corkscrew" vessels. Intraocular pressure was24 mm Hg in the right eye,

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Clinical Histories After Head Trauma*

Patient No./ Age, y/Sex	Pathologic Findings	Time From Injury to Visual Loss	Visual Function: At Time of Trauma	Visual Function: At Time of Visual Loss	Visual Function: After Recovery	Comment
1/21/M	R CC fistula	10 wk	OD, 20/20; OS, NLP	OD, 20/400, central and inferior arcuate; OS, NLP	OD, 20/25, small temporal field defect; OS, NLP	Treatment by intra-arterial balloons
2/18/M	R CC fistula; R ICA aneurysm originating in horizontal intracavernous segment	10 d	OD, 20/200; OS, 20/20	OD, FC 90 cm (3 ft); OS, 20/20	OD, FC 90 cm (3 ft); OS, 20/20 due to CC fistula; no treatment	Orbital apex hemorrhage due to CC fistula
3/26/F	L CC fistula	12 y	OD, 20/20, NL fields; OS, 20/100, nasal island remaining	OD, 20/20, paracentral scotoma; OS, unchanged	OD, 20/20, NL field; OS, unchanged	Treatment by intra-arterial balloons
4/21/F	Intracavernous aneurysm of R ICA; large subfrontal extradural hematoma	8 mo	OD, 20/20; OS, 20/20	OD, 20/30, large paracentral scotoma; OS, 20/20	OD, 20/20, NL field; OS, 20/20, NL field	Epistaxis; treatment: by intra-arterial balloons
5/28/M	Supraclinoid aneurysm of R ICA	8 wk	OD, 20/20, NL field; OS, 20/20, NL field	OD, 20/400, temporal hemianopia; OS, 20/20, NL field	OD, 20/20, NL field; OS, 20/20, NL field	Treatment: intracranial ligation of aneurysm
6/34/M	Intracavernous aneurysm in R ICA	17 y	OD, NLP; OS, NL vision	OD, NLP; OS, 20/50, inferior NFB	OD, NLP; OS, 20/20, field defect improved	Unsuccessful balloon embolization; ICA trapping via intracranial and cervical ligation

*CC indicates carotid cavernous; FC, finger counting; ICA, internal carotid artery; NFB, nerve fiber bundle; NL, normal; and NLP, no light perception.

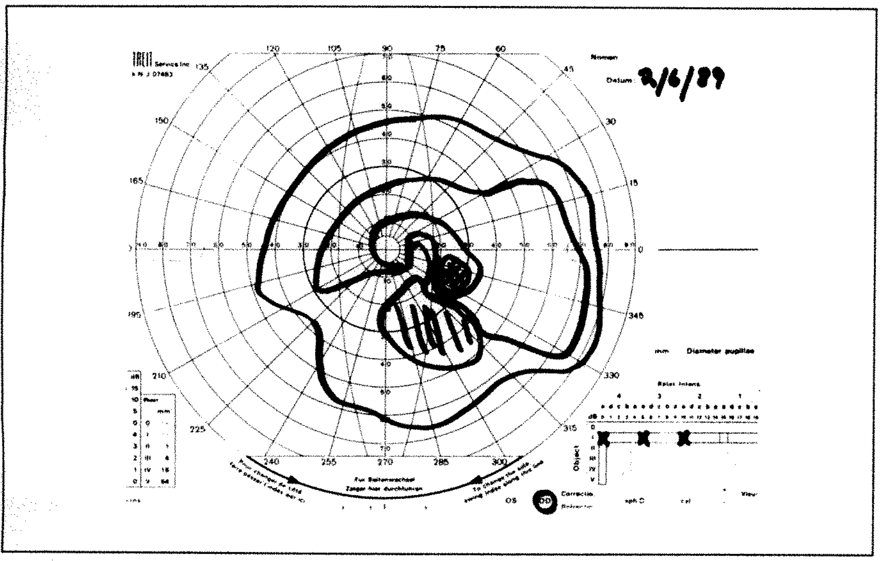

Fig 1.—Visual fields in the right eye of patient 1 showing central and inferior arcuate loss. Vision in the left eye was no light perception.

but it could not be assessed in the left eye because of the tarsorrhaphy. The remainder of the ophthalmologic and general neurologic examination showed normal findings.

Radiologic Studies.—The radiographic examination carried out 6 months after the trauma revealed a large right carotid-cavernous fistula with massive expansion of the cavernous sinus and compression of the suprasellar structures. A computed tomographic (CT) scan with axial and coronal sections confirmed the gross enlargement of the cavernous sinus, predominantly on the right side. The rounded mass entirely filled the suprasellar cistern and extended up and slightly to the left of the midline. There was retrosellar extension indicating dilated inferior petrosal sinuses on both sides. The superior ophthalmic veins were grossly enlarged, on the right more than on the left. Magnetic resonance imaging (MRI) (Fig 2, left) better defined the extent of the dilated cavernous sinus in multiplanar images. The rounded mass appeared to be a thin-walled, aneurysmlike dilation of the cavernous sinus. There was clear evidence of mass effect on the optic pathways with the chiasm draped anteriorly above this varix.

Cerebral arteriography (Fig 2, right) demonstrated that all of the flow from the right internal carotid artery was directed into a carotid-cavernous fistula located at the C3 portion of the siphon. There was immediate filling of the previously described pouchlike extension of the cavernous sinus with immediate opacification of the venous system. The drainage included both inferior petrosal sinuses and, to a somewhat lesser extent, the superior ophthalmic veins, greater on the right than on the left. There was also evidence of retrograde drainage into the cerebral veins. The right external carotid injection demonstrated retrograde flow of the ophthalmic artery, partially feeding the carotid-cavernous fistula. There was collateral flow to the fistula from the left internal carotid artery and vertebrobasilar system via the anterior communicating artery and the posterior communicating artery, respectively. The right posterior communicating artery was markedly bowed upward by the dilated cavernous sinus.

Because the visual loss was felt to be caused by compression of the optic pathways by the pouchlike extension of the cavernous sinus, it was decided not to place detachable balloons within the large fistula itself to avoid substituting the mass effect of balloons for that of the dilated cavernous sinus. For this reason, the fistula was trapped by carotid occlusion with endovascular balloons, which were placed in the internal carotid artery above and below the point of fistulization. There was immediate return of the right posterior communicating artery to its normal position, indicating immediate collapse of the varix.

Follow-up angiography (not shown) and MRI (Fig 3) 4 days after treatment demonstrated persistent collapse of the previously

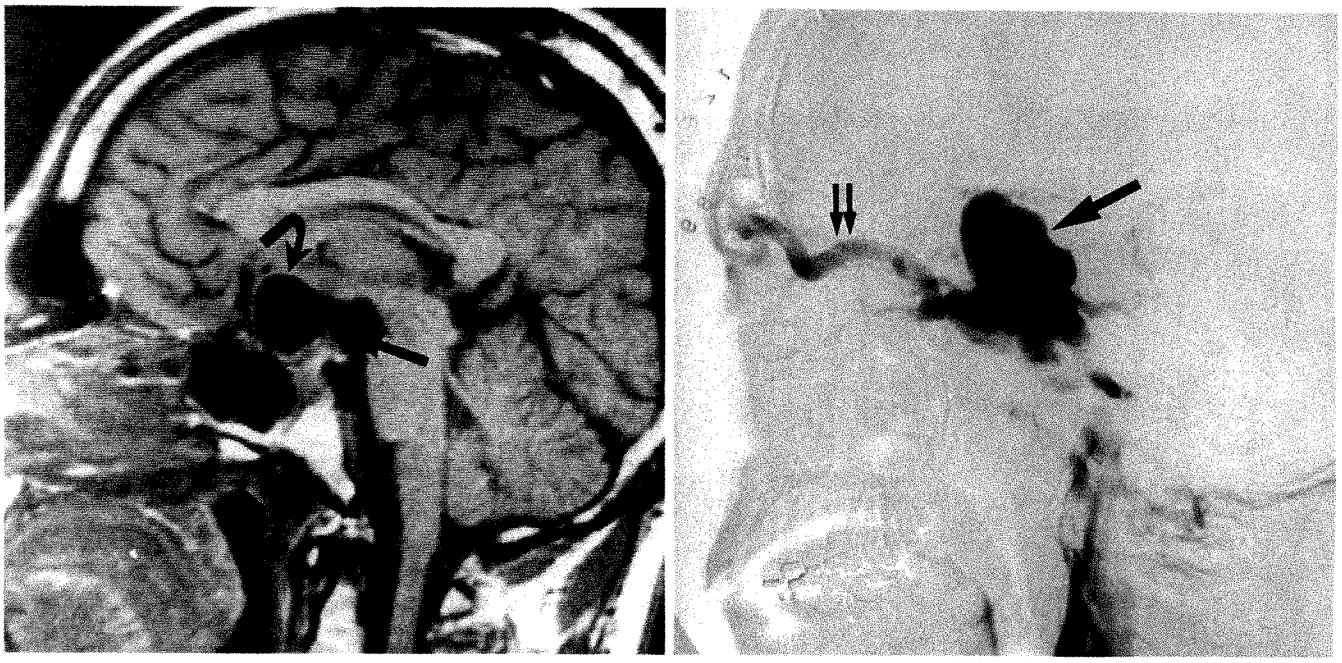

Fig 2.—Sagittal (left) T_1-weighted magnetic resonance image (Signa, General Electric, Schenectady, NY) (1.5 T; TR, 600 milliseconds; TE, 20 milliseconds) and right internal carotid arteriogram (right) of patient 1 at time of presentation. The massively dilated cavernous sinus (single arrows) displaces the optic chiasm (curved arrow) and drains into a dilated right superior ophthalmic vein (double arrows).

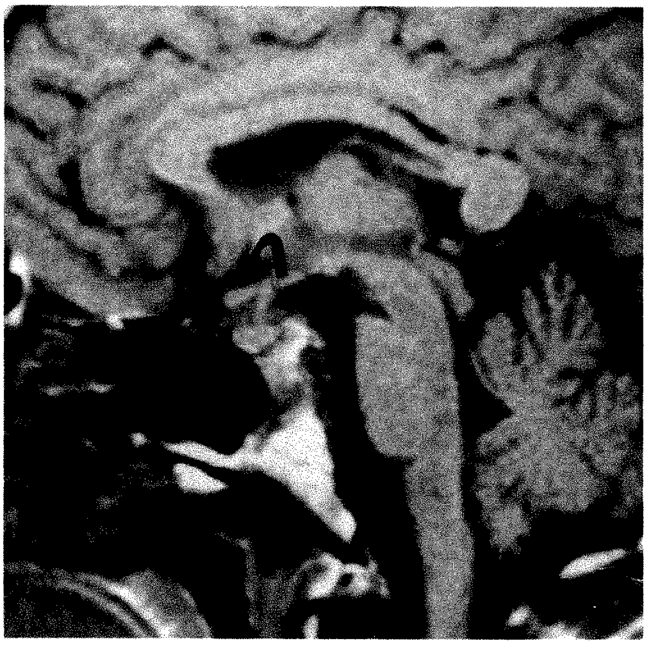

Fig 3.—Sagittal T_1-weighted magnetic resonance image (Signa, General Electric, Schenectady, NY) (1.5 T; TR, 600 milliseconds; TE, 20 milliseconds) of patient 1 four days after right internal carotid occlusion and trapping of fistula. Compare with Fig 2, right. Cavernous sinus has decompressed with return of optic chiasm (curved arrow) to normal position.

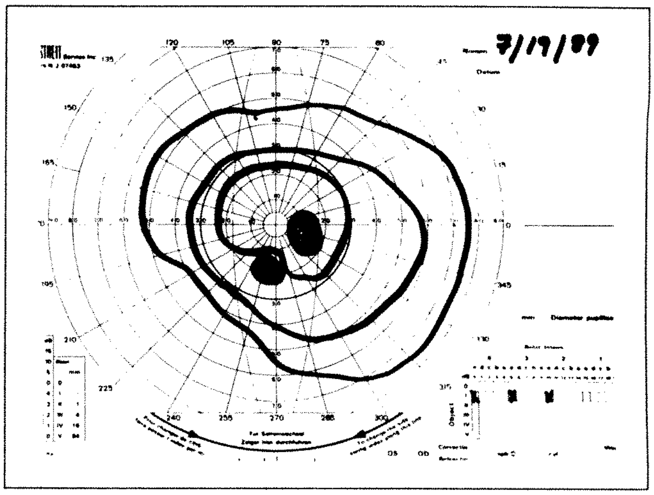

Fig 4.—Visual field in the right eye of patient 1, 5 months after treatment.

dilated cavernous sinus and normalization in the appearance of the intracranial optic pathways.

Clinical Follow-up.—Eighteen hours after angiography and right internal carotid artery occlusion, the patient's visual acuity was 20/25 in the right eye, and there was no light perception in the left eye. The proptosis had diminished, and the episcleral and conjunctival vasculature on the right side was less engorged. The visual fields were improved, though the ocular motility and the appearance of the fundi were unchanged. The bruit was not audible. Results of the reexamination 6 weeks later were unchanged except for a decrease in the caliber of the retinal veins and improvement of visual acuity in the right eye to 20/20. Only a small temporal field defect remained 5 months after the procedure (Fig 4).

CASE 2.—**Clinical History and Examination.**—An 18-year-old man was involved in a motor-vehicle accident on July 5, 1988, and sustained facial and basilar skull fractures, intraventricular hemorrhage, and a right-sided pneumothorax. He was unconscious briefly, and remained in the intensive care unit for 6 days, with gradual improvement in his mental status. When first seen by an ophthalmologist 4 hours after his injury, he was unable to cooperate for tests of visual acuity; pupils were recorded as 4 mm OU in room light with normal light reaction and no afferent defect. Ocular motility was not tested, and results of the fundus examination were recorded as normal. When he was alert

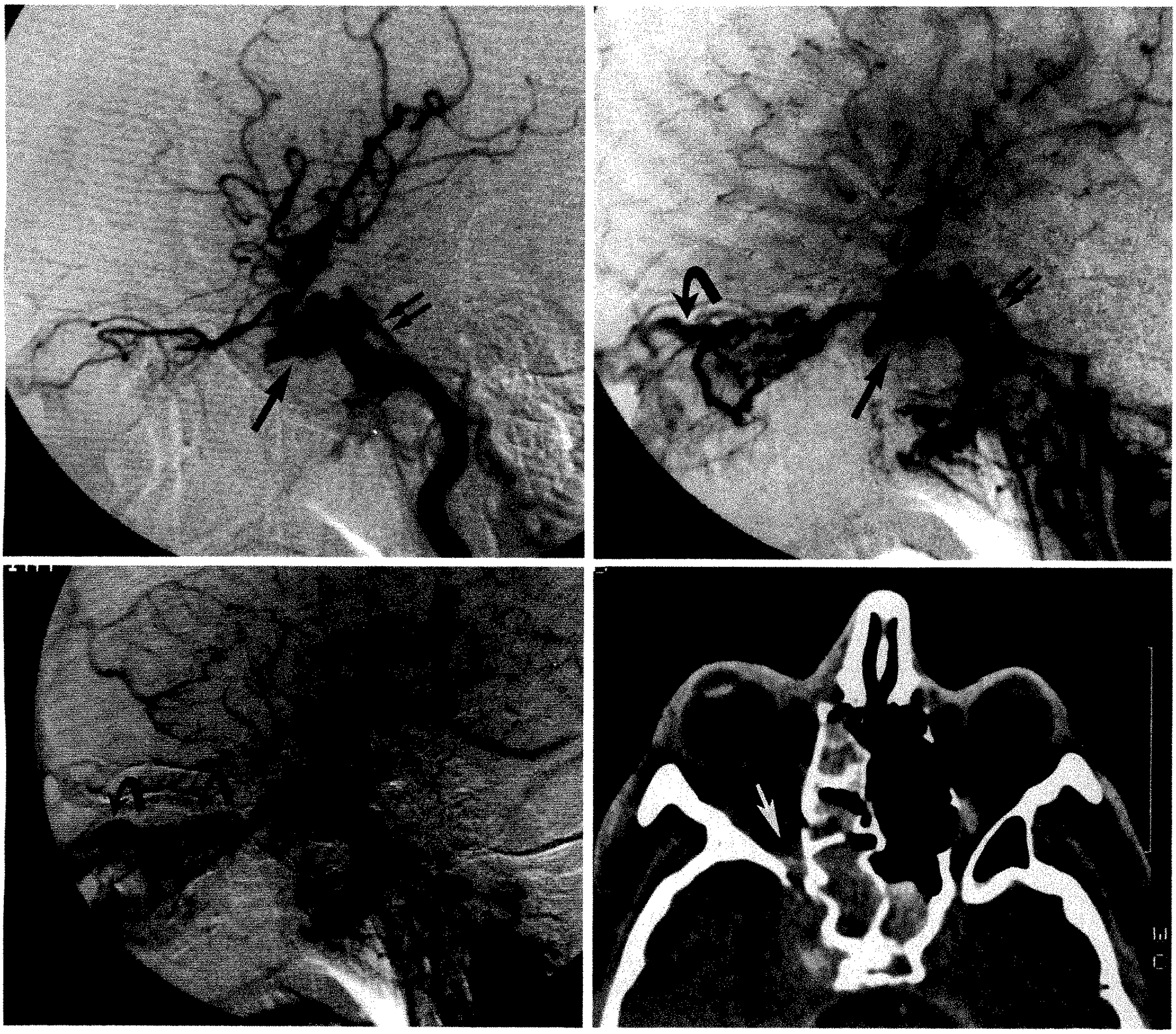

Fig 5.—Early arterial (top left), middle phase (top right), and venous (bottom left) phases from a right internal carotid arteriogram and axial computed tomographic scan through the orbits (bottom right) of patient 2. Note early filling of cavernous (single arrows) and petrosal sinuses (double arrows) and abnormal filling of superior ophthalmic vein (curved arrows), which becomes progressively more distended in bottom left. The superior ophthalmic vein does not drain into the cavernous sinus but appears obstructed at the orbital apex (short arrow). The image shown at the bottom right demonstrates an abnormal soft-tissue density mass in the orbital apex (single arrow), an abnormally enlarged cavernous sinus (curved arrows), and fluid in the ethmoid air cells and sphenoid sinuses.

enough to respond appropriately on the third hospital day, his vision was recorded as 20/200 OD and 20/20 OS. A complete palsy of the right third nerve as well as partial palsies of the right sixth, right seventh, and left sixth nerves were present. Three days later, his visual acuity was recorded as 20/400 OD and 20/20 OS. By the 10th day after the accident, his vision had declined to counting fingers at 120 cm (4 ft) in the right eye, but this was attributed to corneal exposure and use of topical ointments. Eleven days after the accident, vision in the patient's right eye was recorded as counting fingers at 90 cm (3 ft), and there was mild swelling of the right optic disc. Fourteen days after the injury, the visual acuity in the right eye had declined to hand motions, and moderate conjunctival chemosis was present. The patient now noted a bruit in his right ear. Sixteen days after his injury, the patient experienced a sudden bout of epistaxis with approximately 750 mL of blood from the right nostril. Visual acuity in the right eye had declined to light perception. Twenty-four hours after his epistaxis, the patient was transferred to the University of Wisconsin Hospital, Madison.

On examination, visual acuity was bare light perception in the right eye and 20/20 in the left eye. The right pupil was 7 mm and nonreactive, while the left pupil was 3 mm and briskly reactive. A reverse afferent defect (4+) was present on the right side. Confrontation visual fields were full in the left eye, but this test could not be performed in the right eye. Ocular motility of the left eye was normal, but the right eye was immobile except for 2 mm of abduction. An external examination revealed diffuse injection and mild chemosis of the right conjunctiva with no corkscrew vessels. Exophthalmometry readings were 22 OD and 21 OS. Slit-lamp examination findings were unremarkable, and determination of intraocular pressure by Schiotz tonometry was 0 mm Hg OD and 14.6 mm Hg OS. The right optic disc was moderately swollen without spontaneous venous pulsations. The macula, vessels, and periphery were normal. The left optic disc was flat with normal vascularity. The left macula, vessels, and periphery were normal. No per-

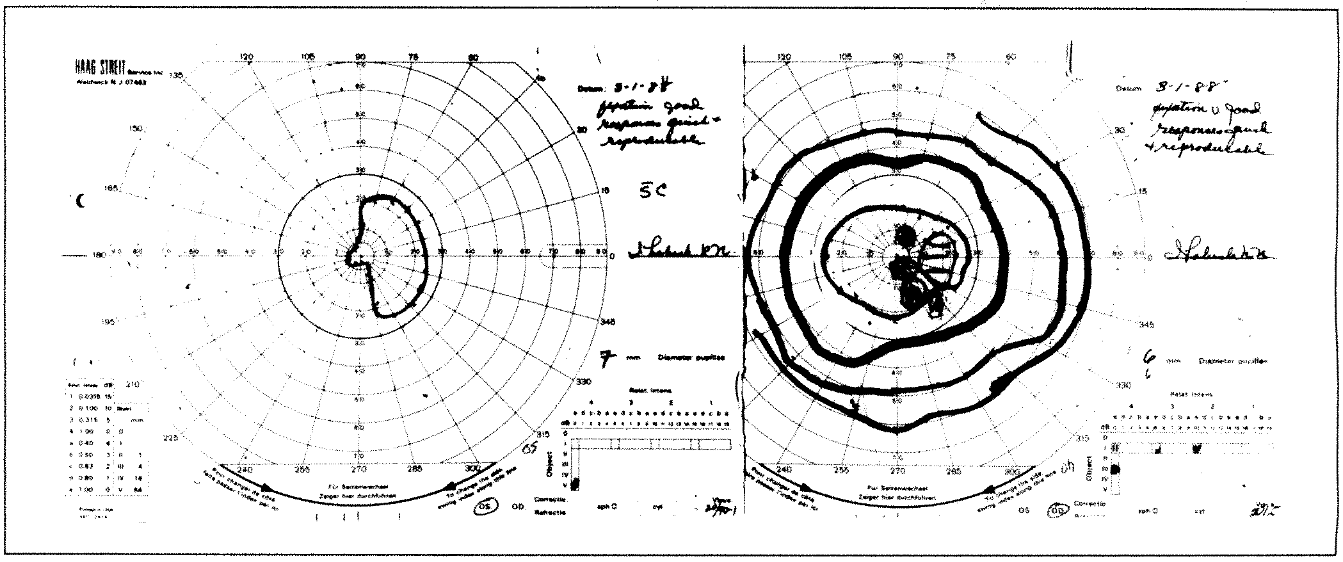

Fig 6.—Visual fields in patient 3 at the time of presentation, 12 years after her injury.

iorbital or cranial bruits were audible, despite the patient's subjective bruit.

Radiologic Studies.—A CT scan performed on July 5, 1988, demonstrated a fracture through the greater wing of the sphenoid bone, extending into the right orbit. There were no extraconal or intraconal orbital lesions. The superior ophthalmic veins were of normal size. There were comminuted fractures of the right ethmoid sinus, and fluid was found in all of the sinuses. A longitudinal fracture extended through the right petrous bone. Pneumocephalus was present, and there was blood in the basilar cisterns. On July 7, 1988, a CT scan showed mild dilation of the right superior ophthalmic vein, but the orbital apex was not imaged in its full vertical extent (middle and superior portions only). An MRI taken on July 13, 1988, demonstrated further enlargement of the right superior ophthalmic vein, extending to the superior orbital fissure, with slight dilation of the right cavernous sinus. However, these changes were not appreciated prior to the onset of epistaxis on July 21, 1988. Carotid arteriography performed on July 22, 1988 (Fig 5), 20 hours after the episode of epistaxis, demonstrated a carotid-cavernous fistula draining primarily toward the right inferior petrosal sinus and partially to the inferior ophthalmic vein through a small communicating vein about the size of the ophthalmic artery. There was delayed filling, via collateral blood vessels, of the right superior ophthalmic vein, which abruptly tapered at the orbital apex and did not empty into the cavernous sinus. These changes were interpreted as consistent with extrinsic compression of the superior ophthalmic vein at the orbital apex, possibly by a hematoma. The mass effect at the orbital apex was confirmed by a CT scan performed on the same day (Fig 5, bottom right).

Clinical Follow-up.—The patient was transferred to the University of Wisconsin Hospital for treatment of the carotid-cavernous fistula. Angiography on arrival demonstrated spontaneous thrombosis of the fistula with only a tiny (<4-mm diameter) pseudoaneurysm remaining. No further treatment was undertaken, and follow-up arteriography performed 12 months later demonstrated a significant decrease in the size of the pseudoaneurysm. Vision has remained 20/20 in the left eye and bare light perception in the right eye.

CASE 3.—**Clinical History and Examination.**—A 26-year-old woman noted blurred vision in her right eye over several weeks. Twelve years previously, she had sustained a basilar skull fracture and traumatic left optic neuropathy in an automobile accident. Vision in the right eye was normal after the accident, and the patient had no further visual complaints until January 1988 when she noted the gradual onset of blurred vision in her right eye and a mild bifrontal headache. She denied symptoms of neurologic dysfunction.

In January 1988, the patient's visual acuity was 20/20 OD and 20/100 OS. Visual fields showed a small nasal island of vision remaining in the left eye and a temporal paracentral scotoma in the right eye (Fig 6). Pupils were equal in size but a left afferent defect (4+) was present. The anterior segment was normal in both eyes, and the intraocular pressures were 12 mm OD and 15 mm OS. There was mild temporal pallor of the right optic disc with normal macula, vessels, and periphery. The left optic disc was extremely pale with normal macula, vessels, and periphery. The remainder of the neurologic examination and general physical examination showed normal findings.

Radiologic Studies.—The radiologic examination revealed a giant, partially thrombosed aneurysm of the left internal carotid artery extending into the suprasellar cistern and compressing the chiasm and intracranial optic nerves. A CT scan performed on January 19, 1988 (not shown), demonstrated a mass in the sellar region encroaching on the left sphenoid sinus. There were secondary bony changes with mottling of the lateral wall of the left sphenoid sinus and elevation of the left anterior clinoid process.

The MRI (Fig 7, left and center) demonstrated the size of the lumen of this partially thrombosed aneurysm to be 1.2 × 1.6 × 2.5 cm. The outer dimensions of the thickened mass proved to be 2.5 × 2.5 × 3.6 cm. The aneurysm extended inferiorly into the sphenoid sinus and superiorly into the suprasellar cistern with elevation of the chiasm and marked deviation of the left optic nerve along the superior lateral aspect of the mass. The thrombosed portions of the aneurysm wall showed a concentric lamination.

Cerebral arteriography demonstrated lateral displacement of the left carotid siphon, with the neck of the aneurysm in the anterior medial portion of the intracavernous segment. Good collateral blood flow to the left cerebral hemisphere was demonstrated. After tolerance of temporary occlusion of the left internal carotid artery, permanent balloon occlusion of the left internal carotid artery was carried out.

Follow-up MRI (not shown) initially demonstrated thrombosis of the aneurysm and the internal carotid artery proximal to the origin of the ophthalmic artery. Subsequent MRIs demonstrated loss of the previously apparent lamination within the wall of the aneurysm with later gradual decrease in size of the mass and marked shrinkage of the thrombosed aneurysm 1.5 years after the endovascular treatment (Fig 8). There was partial restoration of the chiasm toward its normal position.

Clinical Follow-up.—The patient's visual acuity and visual fields were unchanged after undergoing the procedure. Over the ensuing 12 months, the field defect in the right eye gradually and completely resolved. The visual acuity and visual field in the left eye did not change.

COMMENT

Injury to the internal carotid artery may result in partial or complete rupture of any of the vascular layers with resulting dissection,[4] carotid cavernous

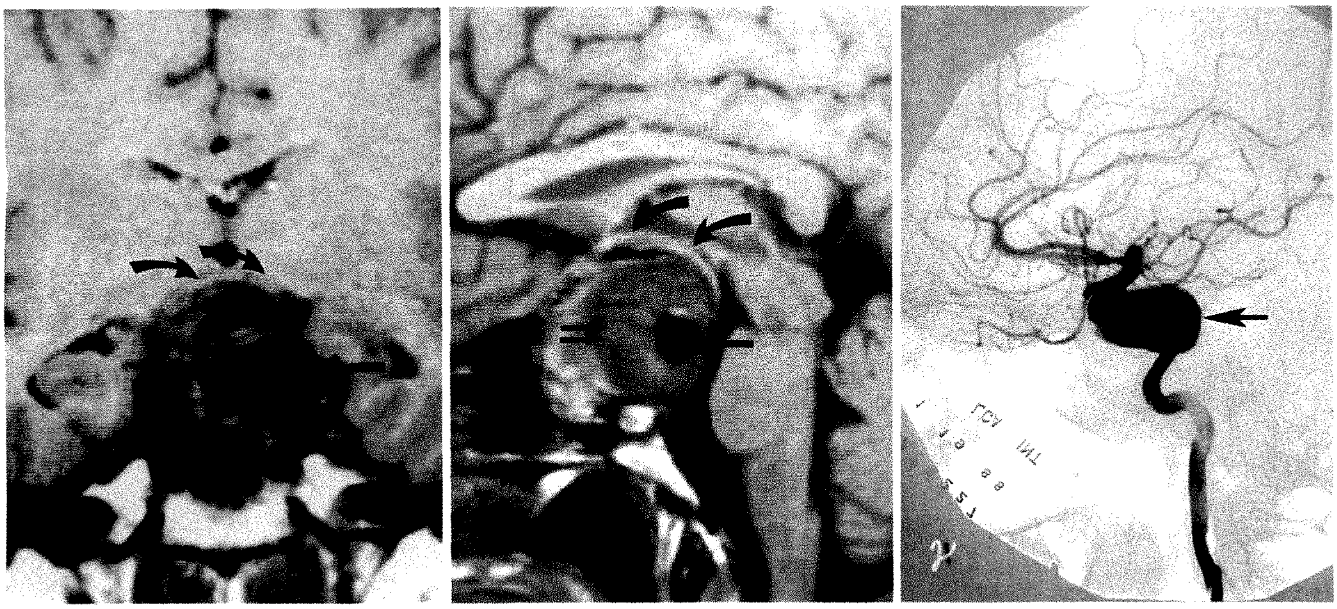

Fig 7.—Coronal (left) and sagittal (center) T_1-weighted magnetic resonance image (MRI) (Signa, General Electric, Schenectady, NY) (1.5 T; TR, 600 milliseconds; TE, 20 milliseconds) and lateral view of a right internal carotid arteriogram (right) of patient 3 at time of presentation. The MRI shows displacement and compression of the optic chiasm (curved arrows) by an aneurysm with a central lumen (single arrows) with mural thrombus (double arrows). Arteriography confirms presence of aneurysm.

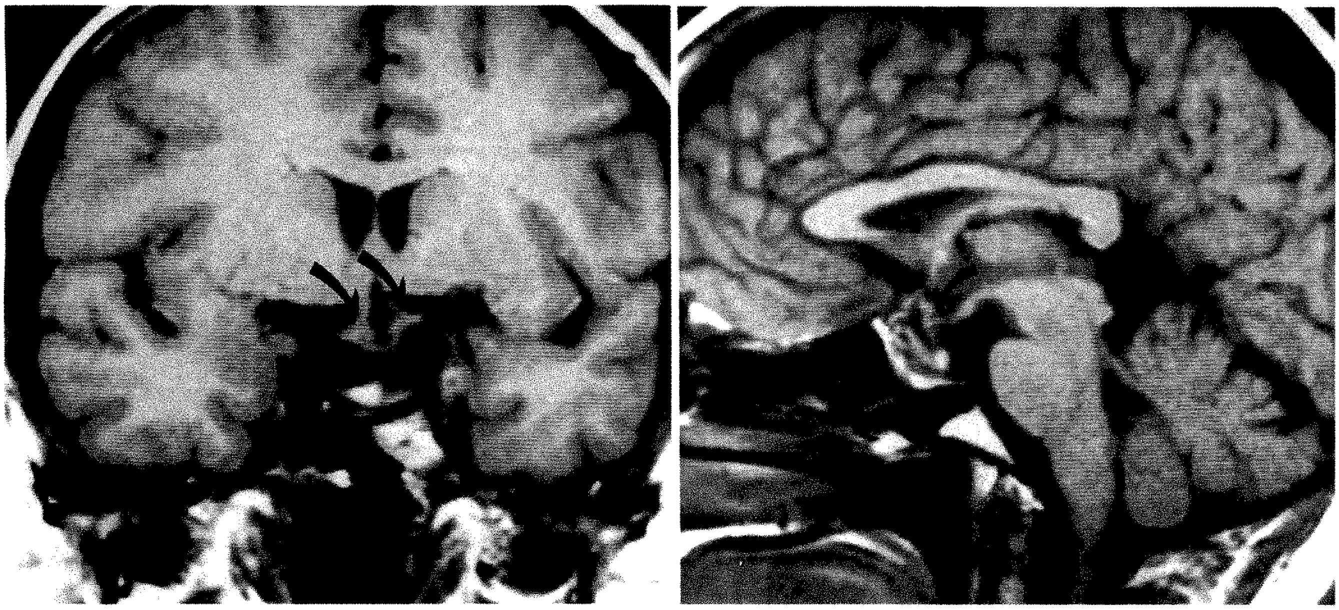

Fig 8.—Coronal (left) and sagittal (right) T_1-weighted magnetic resonance image (Signa, General Electric, Schenectady, NY) (1.5 T; TR,600 milliseconds; TE, 20 milliseconds) of patient three, 1.5 years after treatment. Note the striking resolution of the mass (compare with Figs 7, left and center) with return of the optic chiasm (curved arrows) to a more normal position.

fistula,[5-7] or formation of a false or pseudoaneurysm.[8-11] Distinction between a true aneurysm, false aneurysm, and a pseudoaneurysm is usually not possible without pathologic examination. A traumatic, rather than spontaneous, origin in patients with aneurysms of the carotid siphon region is highly likely when basilar fractures involve the sphenoid and sellar areas (Fig 9) or when a hemorrhage is observed in the sphenoid or posterior ethmoid sinuses or intracranially in the parasellar area. In all of the patients in this study, carotid injury resulted in delayed visual loss due to optic nerve compression. In two patients, visual loss was due to complications arising from a direct carotid-cavernous fistula. Direct compression by the greatly expanded cavernous sinus caused gradual visual loss in patient 1, and hemorrhage at the orbital apex apparently caused rapid visual loss in patient 2. In patients 3 through 6, optic nerve compression resulted from an aneurysm or pseudoaneurysm of the carotid artery. The site of aneurysm formation was the distal intracavernous segment in patients 3 through 5 and the supraclinoid segment in patient 6. In patient 2, an acute visual deficit resulted from periarterial hemorrhage associated with epistaxis. By contrast, visual impairment was not apparent for weeks to years after trauma in the other three patients with aneurysms, apparently because of gradual enlargement of the mass. Recognition of the cause of optic nerve compression led to intervention

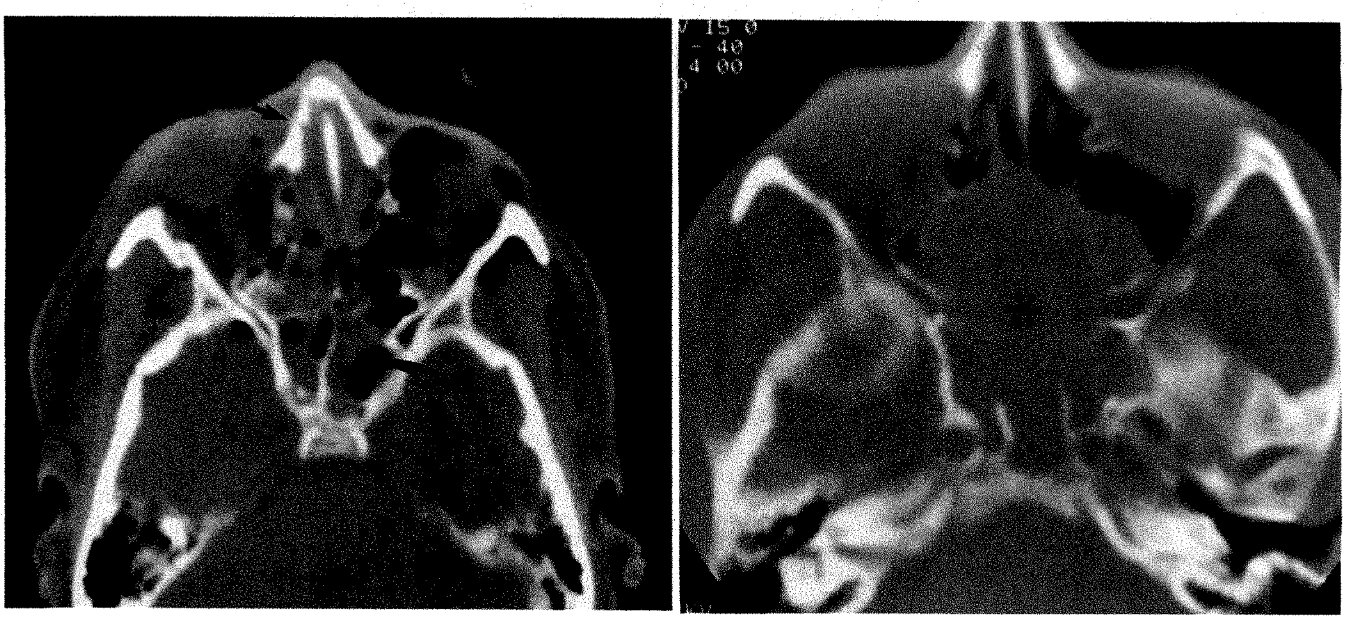

Fig 9.—Axial computed tomographic scans through the skull base, photographed at a bone window setting, at the time of initial injury (left) and at the time of visual loss 10 months later (right) in patient 4. Note the extensive fractures (single arrows), fluid-filled ethmoid and sphenoid sinuses (curved arrows), and small right epidural hematoma containing air (double arrows). The scan at right shows a soft-tissue mass (asterisk) replacing the ethmoid air cells and sphenoid sinus with resorption of the bony septa.

and significant visual recovery in five of six patients with aneurysm or fistula. Visual loss due to carotid-cavernous fistula results most frequently from accompanying glaucoma[15] and less frequently from a form of venous stasis/hypoxic retinopathy.[16-18] In either instance, visual loss may be gradual and delayed. Patient 1 in our series had delayed, but reversible, visual loss due to optic nerve and chiasmal compression from a massively dilated cavernous sinus. Trapping of his fistula with detachable intra-arterial balloons resulted in immediate collapse of the venous pouch and return of vision from 20/400 OD to 20/25 OD within 18 hours, implicating intracranial optic nerve compression, rather than ischemia, as the most probable cause of visual loss. Similar cases have been reported by Dandy and Follis.[19] Hedges et al[7] noted rapid return of visual function after collapse of a fistula using detachable balloons. In their series of 155 patients with carotid cavernous fistulas, Halbach et al[5] identified 21 patients with varices of the cavernous sinus extending into the suprasellar cistern. Details of the visual examination were not given. Three patients experienced fatal subarachnoid hemorrhage, and the authors considered the presence of a varix to be an indication for urgent treatment.

Patient 2 in our series also had delayed visual loss related to a direct carotid cavernous fistula. Angiography suggested extrinsic compression of the superior ophthalmic vein, and the CT scan confirmed the presence of a mass at the orbital apex. This mass had not been seen on prior studies, and we presume that it represented a hematoma compressing the optic nerve, although this radiographic appearance might have been produced by thrombosis of the superior ophthalmic vein. The presence of very low intraocular pressure also suggests the possibility of ophthalmic artery compromise with optic nerve ischemia. Optic nerve ischemia could have been caused by the apical orbital hematoma compressing the ophthalmic artery, although the ophthalmic artery appeared to be of normal caliber angiographically, or by sudden hypotension in the carotid-ophthalmic circulation associated with the episode of epistaxis. The optic disc swelling could, therefore, have been due to compression, ischemia, or ocular hypotony. A case of acute retrobulbar optic nerve ischemia has, in fact, been documented at autopsy in a patient with a carotid cavernous fistula,[18] and we cannot rule out an ischemic component to our patient's visual loss.

Patients 3 through 6 suffered delayed visual loss due to compressive optic neuropathy related to an aneurysm or pseudoaneurysm of the internal carotid artery. In patients 3, 5, and 6, the optic nerve and/or chiasm was directly compressed by the aneurysm. In patient 4, the optic nerve was compressed by an extradural intracranial hemorrhage arising from the pseudoaneurysm. In patients 3 through 5, the pseudoaneurysm arose from the medial portion of the horizontal segment of the carotid siphon, where it is in close approximation to the sphenoid sinus. Epistaxis may be a premonitory sign of damage to the carotid artery at this location and is usually related to extension of the vascular lesion into the sphenoid sinus.[8,9,11-13] Forty-six percent of the cases of carotid pseudoaneurysm reviewed by Chambers et al[8] had their first episode of epistaxis more than 1 month after trauma, and 13% had their first episode at least 6 months after trauma. As pointed out by several authors, this symptom merits thorough investigation in patients with a history of previous head injury.[8,9,11-13,20] In patients 3 and 4, growth of the pseudoaneurysm presumably occurred over intervals of 12 years and 8 months, respectively. This slow growth was reflected in the radiologic appearance of the lesion, with concentric lamination and expansion of adjacent bone. More rapid expansion of the lesion may cause acute visual loss due to extradural hemorrhage within the periarterial tissue. Finally, although delayed epistaxis after head trauma has been considered a warning sign of pseudoaneurysm by most authors, patient 2 in our series demonstrates the fact that delayed epistaxis may also occur in patients with carotid-cavernous fistulas. This sign has also been noted by Halbach et al.[5]

In a comprehensive review of the literature, Chambers et al[8] found reports of 96 patients with the syndrome of delayed epistaxis and immediate (not delayed) monocular blindness due to traumatic pseudoaneurysms of the cavernous internal carotid artery. The authors added four similar cases of their own. One patient presented with epistaxis 40 years after his head trauma. The authors reported a mortality of 30%, with no antemortem diagnosis in 15% of patients and a delay in diagnosis of 4 months or more after epistaxis in 73% of patients. They suggest that more frequent use of carotid arteriography in patients with delayed epistaxis might help to reduce the morbidity and mortality.

Although delayed visual loss was not mentioned in the report of Chambers et al,[8] we are aware of two other reports documenting this complication of traumatic pseudoaneurysms of the internal carotid artery.[12,13] Unfortunately, detailed visual information is not provided in either report. Successful treatment in two of our patients was accomplished by parent artery occlusion with intra-arterial balloons. Elective exclusion of the pseudoaneurysm from the circulation, keeping the artery patent by using an endovascular balloon technique, is preferred when possible. Permanent occlusion of the carotid artery is, nevertheless, recognized as a valid alternative when the morphologic configuration of the pseudoaneurysm does not allow selective treatment.[20] Prior to permanent occlusion of the parent artery, temporary occlusion is performed to determine the patient's tolerance for this procedure.

Patients 2 through 6 in this series had either a fistula or the neck of an aneurysm arising from the medial aspect of the intracavernous portion of the carotid artery siphon. It is unclear why some patients with trauma to this area form carotid-cavernous fistulas while others form pseudoaneurysms. Critical factors determining the type of lesion may include the extent of injury to the various layers of the arterial wall as well as the topographic relationship of the carotid artery to the dural wall of the cavernous sinus and to the bony wall of the sphenoid sinus. Although there were no obvious differences in the site of carotid trauma or the vascular anatomy in our six patients, individual variations in the relationship of the carotid artery to both the cavernous sinus and the sphenoid sinus are well described and are relatively common.[21] If the damaged segment of the arterial wall closely approximates the bony wall of the sphenoid sinus without interposition of the cavernous sinus, or if the artery is surrounded by a hematoma that effectively isolates it from the cavernous sinus, a traumatic aneurysm may be more likely to develop. When the segment containing the arterial tear is completely contained within the cavernous sinus, a fistula is more likely, especially if all layers of the arterial wall are involved. An aneurysm can still develop at this location when the damage to the arterial wall does not involve all layers. Traumatic rupture of small meningeal branches in the cavernous sinus can also result in a fistula supplied by the internal carotid artery or by dural collateral blood flow originating from the external carotid artery. The exact site of the arterial lesion, the configuration of the artery within the cavernous sinus, and its relationship to the sphenoid bone and sinus are all probably important in determining the type of lesion that results when the intracavernous carotid artery is injured.

Clinicians should be highly suspicious of carotid artery injury in patients with severe fractures of the sphenoid and ethmoid sinuses. Clinical and radiologic investigation of these patients should be sufficiently complete to rule out a traumatic carotid aneurysm or a direct carotid-cavernous fistula. A traumatic aneurysm should be suspected in any patient who develops delayed posttraumatic visual loss, even when the visual loss is contralateral to the side of the initial trauma. Intervention may be indicated even in cases with very long intervals between the time of initial trauma and the recognition of compressive optic neuropathy, regardless of the severity of the visual loss or the presence of optic disc pallor.

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References

1. Lessell S. Indirect optic nerve trauma. *Arch Ophthalmol.* 1989;107:382.

2. Kline LB, Morawetz RB, Swaid NS. Indirect injury of the optic nerve. *Neurosurgery.* 1984; 14:756-764.

3. Anderson RL, Panje WR, Gross CE. Optic nerve blindness following blunt forehead trauma. *Ophthalmology.* 1982;89:445-455.

4. Caldwell HW, Hadden FC. Carotid thrombosis: report of 8 cases due to trauma. *Ann Intern Med.* 1948;28:1132-1142.

5. Halbach VV, Hieshima GB, Higashida RT, Reicher M. Carotid cavernous fistulae: indication for urgent treatment. *AJR Am J Roentgenol.* 1987;149:587-593.

6. Debrun GM. Treatment of traumatic carotid-cavernous fistula using detachable balloon catheters. *AJNR.* 1983;4:355-356.

7. Hedges TR, Debrun G, Sokol S. Reversible optic neuropathy due to carotid-cavernous fistula. *J Clin Neuro-ophthalmol.* 1985;5:37-40.

8. Chambers EF, Rosenbaum AE, Norman D, Newton TH. Traumatic aneurysms of cavernous internal carotid artery with secondary epistaxis. *AJNR.* 1981;2:405-409.

9. Shallat RF, Taekman MS, Nagel RC. Delayed complications of craniocerebral trauma: case report. *Neurosurgery.* 1981,8;569-573.

10. Tantana S, Pilla RJ, Awwad EE, Smith KR. Balloon embolization of a traumatic carotid-ophthalmic pseudoaneurysm with control of the epistaxis and preservation of the internal carotid artery. *AJNR.* 1987;8:923-924.

11. Ghorayeb BY, Kopaniky ER, Yeakley JW. Massive posterior epistaxis: a manifestation of internal carotid injury at the skull base. *Arch Otolaryngol Head Neck Surg.* 1988;114:1033-1037.

12. Liu MY, Shih CJ, Wang YC, Tsai SH. Traumatic intracavernous carotid aneurysm with massive epistaxis. *Neurosurgery.* 1985;17:569-573.

13. Van Dellen JR. Intracavernous traumatic aneurysms. *Surg Neurol.* 1980;13:203-207.

14. Marmor M, Wertenbaker C, Berstein L. Delayed ophthalmoplegia following head trauma. *Surv Ophthalmol.* 1982;27:126-132.

15. Phelps CD, Thompson SH, Ossoinig KC. The diagnosis and prognosis of atypical carotid-cavernous fistula (red-eyed shunt syndrome). *Am J Ophthalmol.* 1982;93:423-436.

16. Hostovsky M, Wirtschafter JD, Tubman DE, et al. Reduction of retinal venous tortuosity after detachable balloon occlusion of carotid-cavernous fistulae. *Am J Ophthalmol.* 1941;24:841-843.

17. Sanders MD, Hoyte WF. Hypoxic ocular sequelae of carotid-cavernous fistulae. *Br J Ophthalmol.* 1969;53:82-97.

18. Spencer WH, Thompson HS, Hoyt WF. Ischemic ocular necrosis from carotid-cavernous fistula: pathology of stagnant anoxic 'inflammation' in orbital and ocular tissues. *Br J Ophthalmol.* 1973;57:145-152.

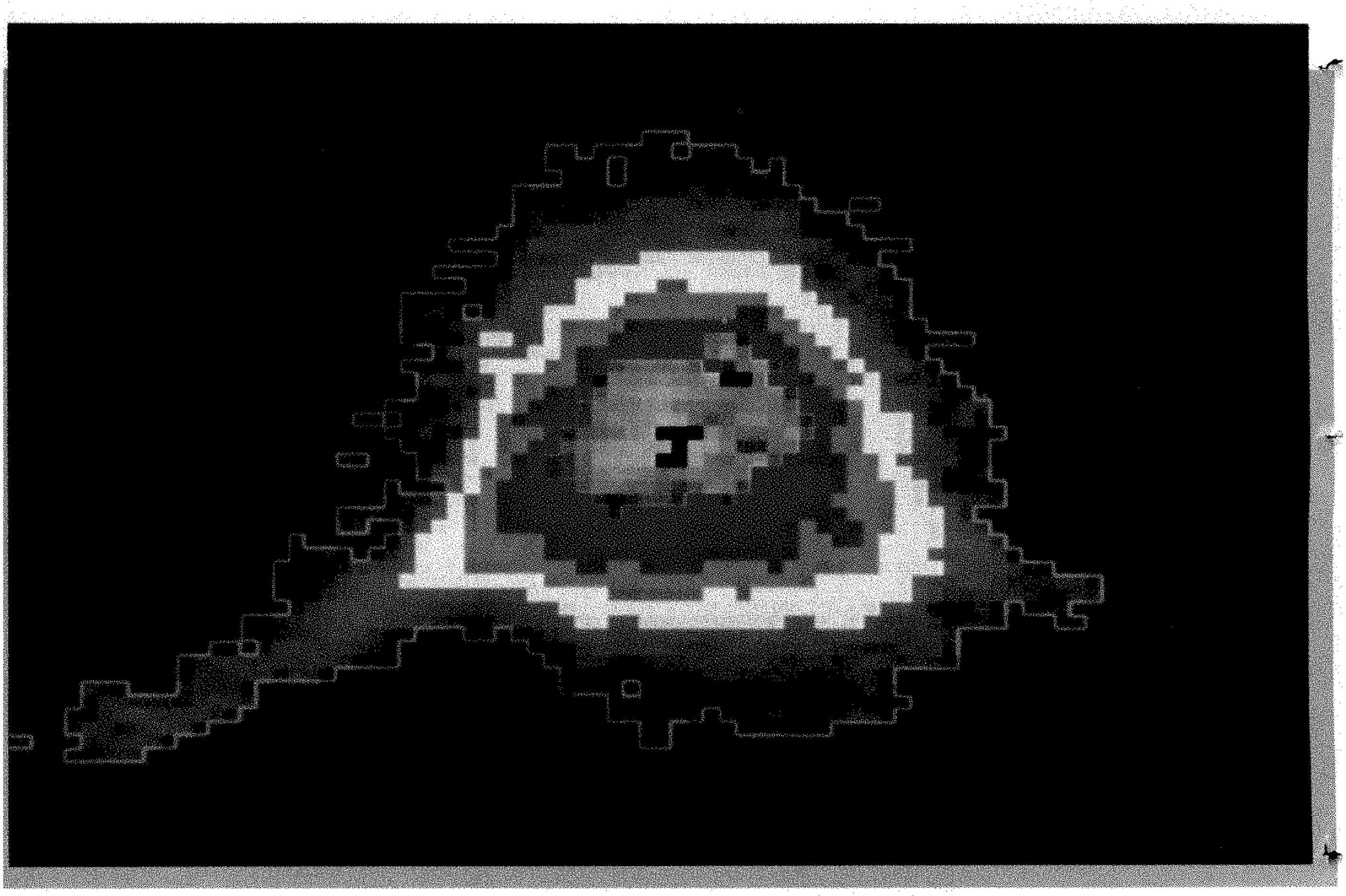
19. Dandy WF, Follis RH. On the pathology of carotid-cavernous aneurysm (pulsating exophthalmos). *Am J Ophthalmol.* 1941;24:365-385.

20. Gelbert F, Reizine D, Stecken J, Rüfenacht D, Laffont J, Merland JJ. Severe epistaxis by rupture of the internal carotid artery into the sphenoidal sinus: endovascular treatment. *J Neuroradiol.* 1986;13:163-171.

21. Bedford MA. The 'cavernous' sinus. *Br J Ophthalmol.* 1966;50:41-46.

Current hypotheses suggest

Calcium influx is a key component of ischemic injury[1-4]

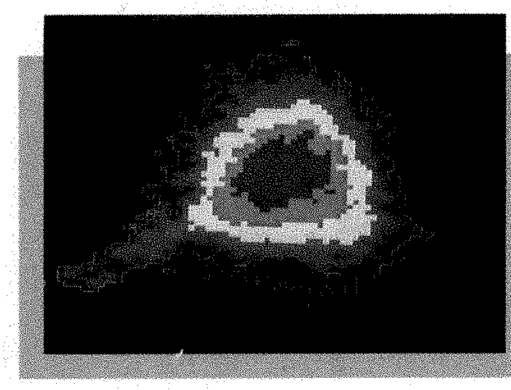


Photomicrograph of depolarized cultured rat hippocampal neuron, showing elevated intracellular calcium. Blue represents lowest and gray represents highest concentration of metabolically active ionized calcium.

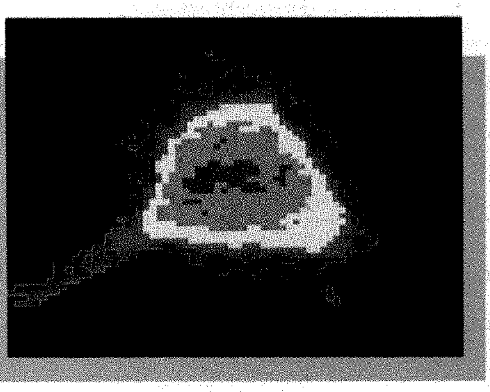
Ischemia is associated with calcium influx which activates phospholipases and degrades neuronal cell membranes[2-4]

Cerebroselective calcium channel blockade may protect against ischemic injury

NIMOTOP modulates calcium influx to promote cerebral perfusion and may directly protect neurons[5-7]



Nimodipine-treated cultured rat hippocampal neuron under depolarizing conditions, showing decreased intracellular calcium.



Cultured rat hippocampal neuron showing normal intracellular calcium[8]

In aneurysmal subarachnoid hemorrhage

CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

Reduces the consequences of cerebral ischemia

In aneurysmal subarachnoid hemorrhage

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Reduces the consequences of cerebral ischemia

BRIEF SUMMARY
NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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REFERENCES: 1. Gelmers HJ. The role of calcium and the significance of calcium antagonists in some neurological and neurosurgical diseases. *Clin Neurol Neurosurg.* 1983;85:213-224. **2.** Siesjö BK. Calcium, ischemia, and death of brain cells. *Ann NY Acad Sci.* 1988;522:638-661. **3.** Hoff JT. Cerebral protection. *J Neurosurg.* 1986;65:579-591. **4.** Hubschmann OR. The role of calcium in parenchymal cell injury in subarachnoid haemorrhage. *Neurolog Res.* 1987;9:265-269. **5.** Scriabine A, van den Kerckhoff W. Pharmacology of nimodipine. A review. *Ann NY Acad Sci.* 1988;522:698-706. **6.** Petruk KC, West M, Mohr G. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg.* 1988;68:505-517. **7.** Uematsu D, Greenberg JH, Hickey WF, Reivich M. Nimodipine attenuates both increase in cytosolic free calcium and histologic damage following focal cerebral ischemia and reperfusion in cats. *Stroke.* 1989;20:1531-1537. **8.** Data on file, Miles Inc.

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Acute Pseudobulbar or Suprabulbar Palsy

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• We studied 13 patients with supranuclear lower cranial nerve ("pseudobulbar" or "suprabulbar") palsy of acute onset. While seven patients had had a prior stroke, six patients had no history of stroke. Eight patients experienced a complete bilateral supranuclear lower cranial nerve palsy, which was isolated in five patients and associated with hemiplegia and with hemiparesis in three patients. Pseudobulbar palsy was partial in five patients. Only one patient had neuropsychologic impairment. The pseudobulbar features improved or recovered within a few weeks in all patients. The common characteristic of the lesions on computed tomography or magnetic resonance imaging was the interruption of the corticonuclear pathways contrasting with marked sparing of the corticospinal pathways in both hemispheres. These lesions were either an opercular infarct, or a deep infarct in the corona radiata or internal capsule, or a lenticular hemorrhage. Hypertension was the most prevalent concomitant. Our findings suggest that acute pseudobulbar or suprabulbar palsy has rather stereotyped anatomic-vascular correlates and time course.

(*Arch Neurol.* 1991;48:501-507)

The term *pseudobulbar palsy* was coined in 1877 by Lépine[1] to differentiate lower cranial nerve palsy induced by supranuclear lesions from bulbar palsy related to bulbar nuclei lesions. Supranuclear lesions included corticobulbar and corticopontine pathway lesions. However, in 1837, Magnus[2] reported the first case of pseudobulbar palsy due to multiple infarcts and a few other cases have also been reported.[3,4] Several clinical and anatomic studies were performed at the beginning of the 20th century, and in his 1929 thesis Thurel[5] summarized the current knowledge at that time. He divided pseudobulbar palsy into three forms. The cortical form (Foix-Chavany-Marie syndrome[6]) was characterized by a faciopharyngoglossomasticatory diplegia with automatic voluntary dissociation. In the striatal form, the same features were associated with pyramidal signs, emotional lability, and intellectual impairment. The pontine form was characterized by faciopharyngoglossomasticatory diplegia associated with emotional lability, pyramidal and sometimes cerebellar signs, and by a lack of dementia. The term *pseudobulbar* was descriptive. In 1940, Langworthy and Hesser[7] coined the term *supranuclear bulbar paralysis* with reference to the suprabulbar location of lesions. Because the facial nucleus and the trigeminal motor nucleus are in the pons and patients may present facial diplegia or masticatory palsy, the terms *supranuclear pontobulbar palsy* or *corticobulbopontine palsy* are more appropriate. It may be easier to use the term *suprabulbar palsy*, as suggested by Loeb et al.[8] However, contrary to pseudobulbar all these terms fail to identify the bulb as the location of the symptoms. Also due to historic reasons, the term *pseudobulbar* is more widely used than *suprabulbar*.

In most patients, pseudobulbar palsy developed by fits and starts in relation to multiple recurrent strokes. We studied 13 patients in whom pseudobulbar palsy developed acutely.

PATIENTS AND METHODS

Patients were identified among 1800 stroke patients from the prospective Lausanne (Switzerland) Stroke Registry.[9] Seven patients had had a stroke prior to acute pseudobulbar palsy (group 1), while in six patients, acute pseudobulbar palsy developed without prior stroke (group 2). Computed tomography (CT) or magnetic resonance imaging (MRI) were performed in all patients, as well as extracranial Doppler ultrasound, electrocardiogram, standard blood tests, and neuropsychologic examination with a standard battery of tests.[10] Transcranial Doppler ultrasounds were performed in seven patients and cerebral angiography (Seldinger technique) was performed in one patient. Bidimensional echocardiography was performed in three patients. Vascular concomitants, such as hypertension (blood pressure higher than 160/90 mm Hg at least twice before the stroke), diabetes mellitus (fasting serum glucose concentration higher than 5.6 mmol/L), hypercholesterolemia (cholesterol higher than 6.5 mmol/L), and history of cigarette smoking were analyzed following the guidelines of the Lausanne Stroke Registry.[9]

REPORT OF CASES

CASE 1.—A 79-year-old man with a history of hypertension, atrial fibrillation, and aortic valve prosthesis experienced a left central facial paresis, which recovered over 1 month. A year later, he suddenly developed dysphagia and dysarthria. On admission, his blood pressure was 250/130 mm Hg. A left lower facial weakness was noted, while facial sensation was normal and corneal reflexes were symmetrical. We noted that his soft palate drooped bilaterally and the gag reflex was absent. Tongue movements were slowed with impaired protrusion. Examination of the sternocleidomas-

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Table 1.—Radiologic Findings*

Patient	Right Hemisphere	Left Hemisphere
Group 1		
1	*SDI in rostral part of posterior limb of IC*	SDI in rostral part of posterior limb of IC
2	SDI in rostral part of posterior limb of IC	*SDI in rostral part of posterior limb of IC*
3	*Opercular superficial MCA infarct*	Opercular superficial MCA infarct
4	Multiple SDI	Multiple SDI
5	SDI in medial part of CR	*SDI in medial part of CR*
6	SDI in anterior part of CR	*SDI in medial part of CR*
7	*Lenticulocapsular hemorrhage*	Opercular superficial MCA infarct
Group 2		
8	SDI in posterior part of CR	SDI in medial part of CR
9	SDI in rostral part of posterior limb of IC	SDI in rostral part of posterior limb of IC
10	Opercular superficial MCA infarct	SDI in medial part of CR
11	Opercular superficial MCA infarct	SDI in medial part of internal capsule
12	SDI in genu limb of internal capsule	SDI in genu of internal capsule
13	SDI in medial part of CR	Opercular superficial MCA infarct

* SDI indicates small, deep infarct; CR, corona radiata; IC, internal capsule; MCA, middle cerebral artery; and new lesion is italicized.

toid and trapezius muscles was normal. Jaw reflex was brisk. The patient was dysarthric and had a hypernasal voice. He chewed and swallowed with difficulty. No motor or sensory deficit was present in the limbs and trunk. Plantar responses were flexor. Results of a neurologic examination, 2 weeks after the onset, were normal.

Case 2.—A 71-year-old hypertensive and diabetic woman experienced right-sided weakness lasting for 30 minutes. A month later, she suddenly developed right-sided weakness and numbness that improved during the following day. The next morning, she lost consciousness and fell down. On awakening, she had a left-sided sensory-motor hemiparesis. On admission, her blood pressure was 210/100 mm Hg. Left lower facial weakness was noted. Sensory examination of her face and mouth was normal and corneal reflexes were symmetrical. The voice was low pitched, but there was no dysarthria. Pharyngeal motility, gag reflex, and swallowing were normal. Tongue movements were slowed and limited in range. Examination of the sternocleidomastoid and trapezius muscles was unremarkable. Jaw and palmomental reflexes were brisk. Left-sided spastic hemiparesis with brisk tendon reflexes and Babinski's sign was present. Sensation was decreased for touch, pinprick, position sense, graphesthesia, and pallesthesia on the left side. The patient was discharged after 2 weeks with only a persisting left hemiparesis.

Case 3.—A 40-year-old woman suffered a stroke with left hemiplegia. One year later, she was hospitalized in another institution for clonic movements of the lips followed by a generalized tonicoclonic seizure. On admission, 5 days after the seizure, her blood pressure was 130/80 mm Hg. Neurologic examination showed a severe facial diplegia, the mouth was open and she dribbled. Jaw reflex was brisk. Facial and buccal sensation were normal. The soft palate was immobile and the gag reflex was absent. She was unable to chew, to swallow, to speak, or to protrude her tongue. The sternocleidomastoid muscle was bilaterally weak. She had episodes of laughing and crying. The rest of the neurologic examination showed a left spastic hemiparesis with brisk tendon reflexes and Babinski's sign. She was discharged 6 weeks after the onset with only a mild improvement of the facial diplegia.

Case 4.—A 70-year-old hypertensive woman was admitted for sudden headaches followed by dysphagia and dizziness. Eight years before, she had experienced a left hemiplegia with left-sided sensory impairment. The hemiplegia had completely recovered, but she continued to complain of pins and needles sensation on the left side. On admission, her blood pressure was 190/120 mm Hg. Corneal reflex and facial pain and temperature sensation were decreased on the left side. Left lower facial weakness was present. Examination of the palate and tongue was normal, but she was unable to swallow and frequently coughed on her saliva. The gag reflex was present. The sternocleidomastoid and trapezius muscles were normal. The remainder of the neurologic examination showed mild weakness of the left arm and leg, brisk tendon reflexes, and left-sided Babinski's sign. The patient was discharged 4 weeks after the onset with a mild dysphagia.

Case 5.—A 74-year-old man with a history of hypertension, diabetes mellitus, and hypercholesterolemia was admitted for sudden dysarthria and dysphagia. Two years before, he had been seen in our department for a right ataxic hemiparesis. On cranial nerve examination at that time, he had rightward deviation of the tongue on protrusion. Computed tomography showed a small, deep infarct in the left capsulothalamic area. Six months later, he was readmitted for a right motor hemiparesis. Computed tomography showed a second small infarct in the medial part of the left corona radiata. Clinical recovery was complete and the patient remained asymptomatic for 18 months. On the present admission, his blood pressure was 170/100 mm Hg. Left lower facial weakness was present, while sensory examination of face was normal. He had severe dysphagia and dysarthria. The soft palate was weak bilaterally. Examination of the tongue, trapezius, and sternocleidomastoid muscles was normal. He had left mild hemiparesis without Babinski's sign. The patient recovered from the hemiparesis within 2 months, while the other signs persisted.

Case 6.—A 76-year-old hypertensive diabetic man with a history of shunted hydrocephalus developed a right hemiparesis. Cranial nerve examination was normal, CT showed a left capsular infarct. He was left with mild hemiparesis until 4 years later when he was admitted for sudden dysphagia and dysarthria. On admission, his blood pressure was 160/100 mm Hg. Neurologic examination showed facial diplegia without facial sensory abnormality or corneal reflex asymmetry. The jaw reflex was very brisk. The soft palate drooped bilaterally, more so on the left side, and the gag reflex was abolished. The patient was unable to chew and to swallow, and he had severe dysarthria. On protrusion, the tongue deviated to the left. The left hemiparesis was still present and plantar response was extensor bilaterally. The patient was discharged after 2 months with persisting facial diplegia, bilateral soft-palate weakness, and dysarthria.

Case 7.—A 73-year-old hypertensive man with a history of myocardial infarction suffered a left middle cerebral artery infarction with right sensory motor hemiplegia and aphasia. Angiography showed a 50% stenosis of the left internal carotid artery. Five years later, left internal carotid occlusion was discovered on a Doppler checkup. Nine years later, he was admitted for sudden mutism. On admission, his blood pressure was 170/90 mm Hg. Neurologic examination showed facial diplegia. Eye closure was weak, while the corneal reflex was asymmetric but present. The masticatory muscles were weak bilaterally. The patient's mouth remained open and he dribbled. He was mute and could not swallow. The jaw reflex was brisk. The palate was immobile and drooped. The gag reflex was absent. Tongue protrusion was markedly weak without deviation. Bilateral weakness of the sternocleidomastoid and trapezius muscles was present. The remainder of the neurologic examination was normal, including plantar responses. Two months after the onset, the patient could swallow and speak. His voice was dysarthric and all other signs persisted.

Case 8.—A 77-year-old hypertensive woman was admitted for sudden left hemiplegia. On admission, her blood pressure was 140/80 mm Hg. She had a vertical gaze paresis, while her horizontal gaze was normal. There was a left lower facial paresis without abnormal facial sensation. The soft palate was immobile and the gag reflex was absent. There was a leftward deviation of the tongue on protrusion. The left trapezius and sternocleidomastoid muscles were weak. Swallowing was impaired and the voice was hoarse. Left hemiplegia and right hemiparesis were present. Tendon reflexes were brisk and plantar responses were extensor bilaterally. The patient was discharged after 4 weeks. The left hemiplegia persisted unchanged, while the right hemi-

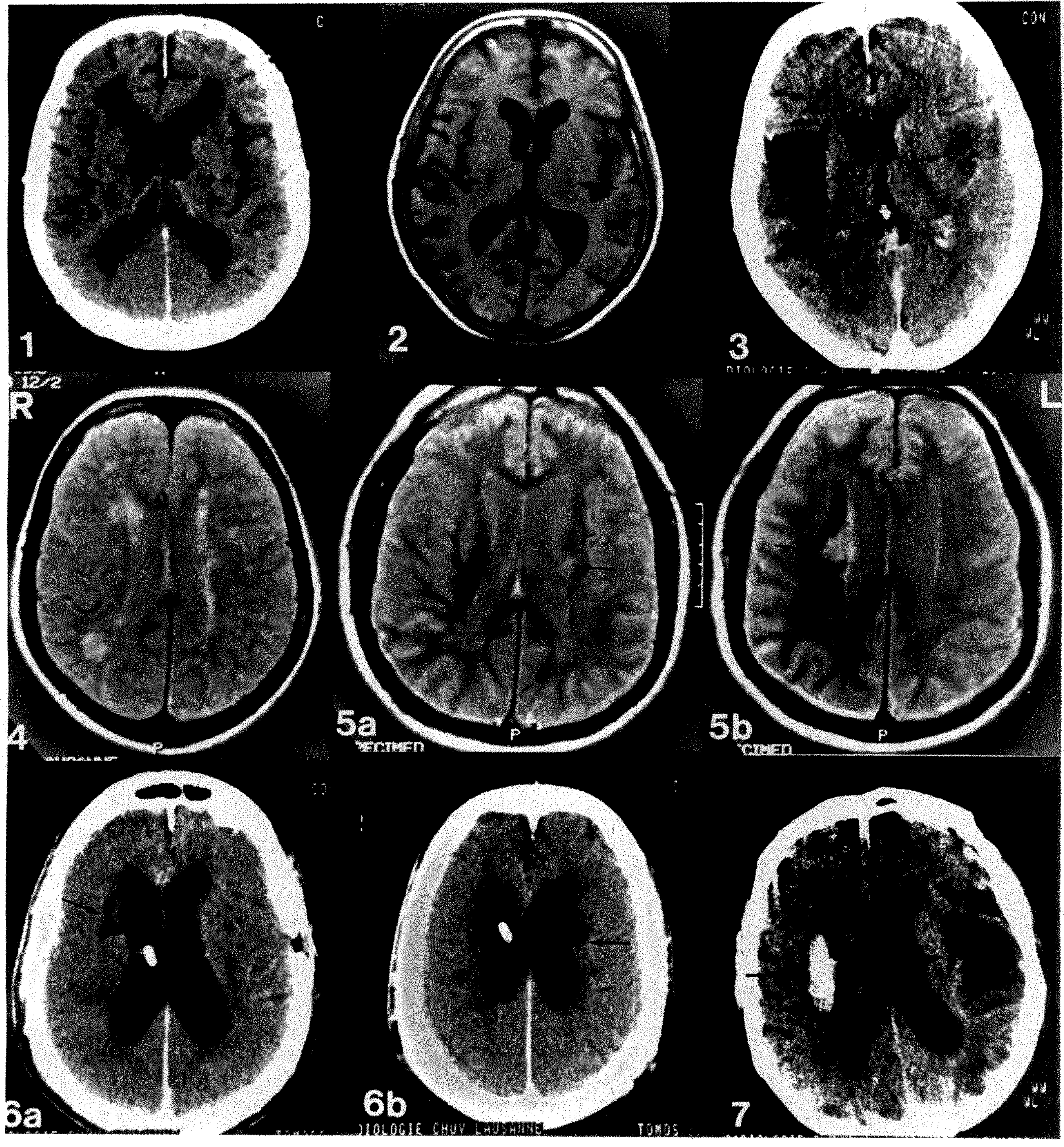

Fig 1.—Group 1. Computed tomographic or magnetic resonance imaging findings (R indicates right; L, left; and arrows point to the lesions). Number 1 through 7 refer to patients 1 through 7 mentioned in Table 1.

paresis and other signs improved.

Case 9.—A 55-year-old man experienced mild head trauma without loss of consciousness, but he subsequently complained of dysphagia and dysarthria. On admission, 8 days later, his blood pressure was 240/130 mm Hg. A right lower facial paresis was noted. Sensory examination of the face and soft palate was normal. Tongue movements were slowed and decreased in amplitude. Swallowing was difficult, but pharyngeal motility and gag reflex were normal. The patient had dysarthria and his voice was hypernasal. The remainder of the neurologic examination was normal, including plantar responses. The patient improved over 2 weeks and was discharged with persisting dysarthria.

Case 10.—A 71-year-old hypertensive woman experienced transient dysarthria. Two days later, she developed progressive left hemiparesis. One day later, she developed sudden dysarthria and severe dysphagia. On admission, her blood pressure was 140/90 mm Hg. Severe facial diplegia was present. The jaw reflex was brisk. Left facial hypesthesia for touch, pain, and temperature was present. The left corneal reflex was absent. The soft palate drooped bilaterally and the gag reflex was abolished. Tongue protrusion was slow and weak. The patient was dysarthric, with a low-pitched voice. She was unable to chew and to swallow. Left hemiparesis with brisk tendon reflexes and left-sided Babinski's sign was present. Pinprick and temperature sensa-

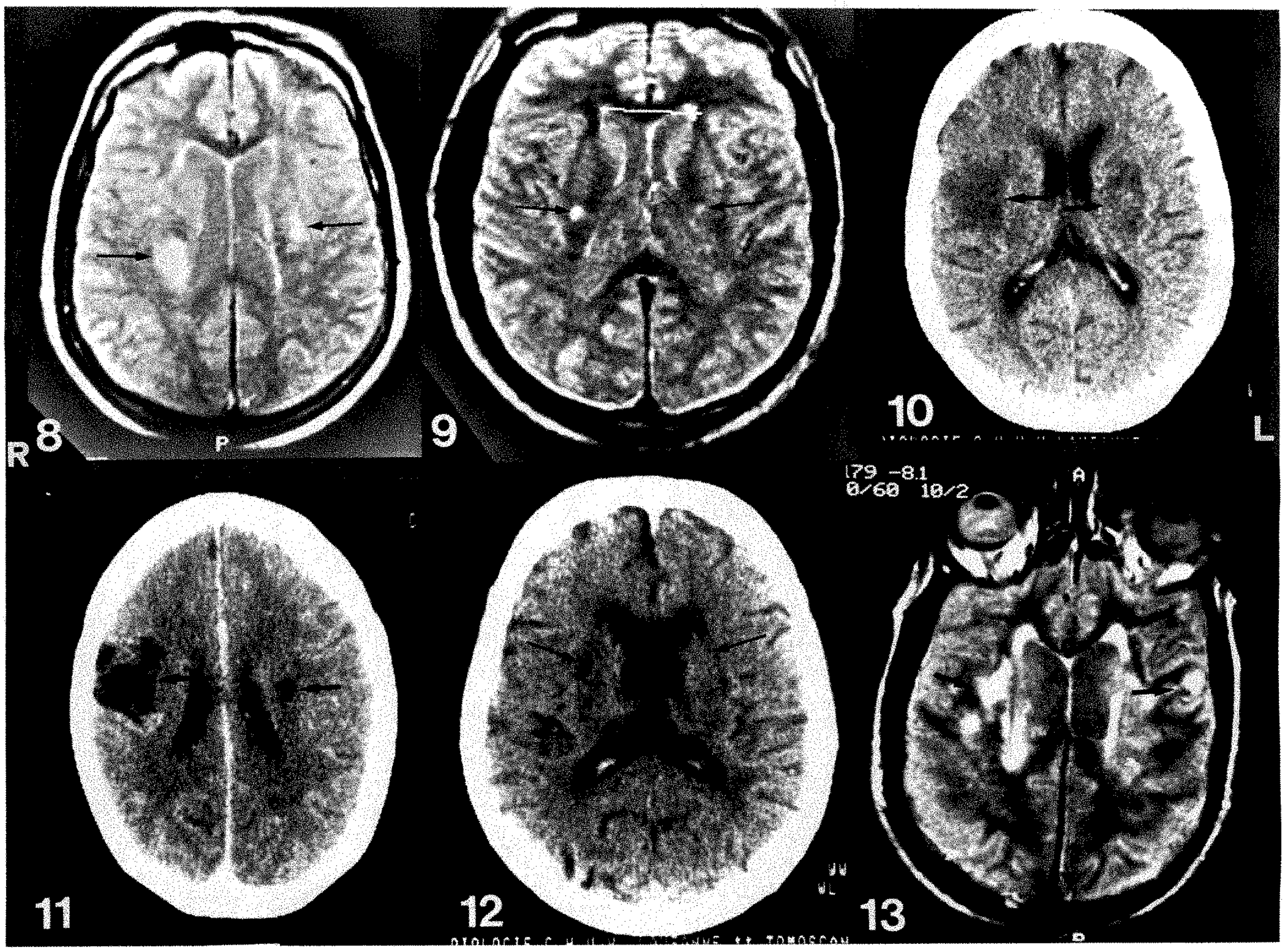

Fig 2.—Group 2. Computed tomographic or magnetic resonance imaging findings (R indicates right; L, left; and arrows point to the lesions). Number 8 through 13 refer to patients 8 through 13 as mentioned in Table 1.

Table 2.—Neurologic Findings*

Patient/Sex/Age, y	History	FP	PP	GR	TP	DP	DR	JR	XI
1/M/68	Left facial paralysis	B	B	A	B	+	+	Brisk	N
2/F/71	Transient left hemiparesis	L	N	P	B	−	−	Brisk	N
3/F/40	Left hemiparesis	B	B	A	B	+	+	Brisk	B
4/F/70	Left hemiparesis	L	N	P	N	+	−	Normal	N
5/M/64	Right AHP	L	N	P	N	+	+	Normal	N
6/M/66	Right PMH	B	B	A	L	+	+	Brisk	N
7/M/73	Right hemiparesis	B	B	A	B	+	+	Brisk	N
8/F/78	. . .	L	B	A	R	+	+	Normal	L
9/M/55	. . .	R	N	P	B	+	+	Normal	N
10/F/70	. . .	B	B	A	B	+	+	Brisk	N
11/F/63	. . .	B	B	A	B	+	+	Brisk	N
12/M/74	. . .	B	L	A	N	+	+	Brisk	N
13/M/81	. . .	B	B	A	B	+	+	Brisk	N

*FP indicates facial paralysis; PP, palate paralysis; GR, gag reflex; TP, tongue paralysis; DR, dysarthria; DP, dysphagia; JR, jaw reflex; XI, XIth nerve palsy; AHP, ataxic hemiparesis; PMH, pure motor hemiparesis; M, male; F, female; A, abolished; B, bilateral; P, present; L, left; N, none; R, right; plus sign, present; and minus sign, absent.

tion were reduced on the left side. The dysphagia completely recovered within 2 months, while mild hemiparesis and the other signs persisted.

Case 11.—A 63-year-old hypertensive woman had a 46-year history of left partial motor seizures starting in the left arm and sometimes followed by generalized clonic movements. She was admitted for sudden dysphagia and dysarthria. On admission, her blood pressure was 140/90 mm Hg. There was a facial diplegia. Her mouth remained open and she dribbled. The masseter muscles were weak. The jaw reflex was brisk. The soft palate drooped and she had decreased sensation on the right side. The gag reflex was absent. Motility of the vocal cords was normal on laryngeal examination. Tongue movements were severely limited in range and in strength. The patient was unable to chew and to swallow and her voice was low pitched and hypernasal. The rest of the neurologic examination was normal except for a mild left pronator drift. Plantar responses were bilaterally flexor. The patient improved over 3 weeks and was discharged with only a moderate left palate and lower facial paresis.

Case 12.—A 74-year-old hypertensive man with a history of myocardial infarction was admitted for sudden dysarthria and dysphagia. On admission, his blood pressure was 150/90 mm Hg. There was a bilateral lower facial paresis. The jaw reflex was brisk. Sensory examination of the face was unremarkable and the corneal reflex was normal. The soft palate was weak on the left side. The gag reflex was abolished. No tongue, trapezius, or sternocleidomastoid muscle weakness was present. Swallowing and chewing were impaired. His voice was dysarthric and low pitched. The rest of the neurologic examination was normal, in-

Table 3.—Vascular Concomitants*

Patient	Cardiac Disease	Hypertension	Diabetes	Smoking	Elevated Cholesterol	Doppler Extracranial	Doppler Transcranial
1	Prosthetic aortic valve, AF	+	–	–	+	Normal	Not done
2	No	+	+	–	+	Normal	Not done
3	No	–	–	+	–	Normal	Normal
4	No	+	–	–	–	Normal	Not done
5	No	+	+	–	+	Normal	Normal
6	No	+	+	–	–	Normal	No detection right ACA
7	Old myocardial infarction	+	–	–	–	Left ICA occlusion	Normal
8	No	+	–	+	–	Normal	Normal
9	No	+	–	+	–	Normal	Normal
10	No	+	–	–	–	Right ICA occlusion	Not done
11	No	–	–	–	+	Normal	Normal
12	Old myocardial infarction	+	–	+	–	Normal	Not done
13	No	+	–	–	–	Normal	Not done

*AF indicates atrial fibrillation; ACA, anterior cerebral artery; ICA, internal carotid artery; plus sign, present; and minus sign, absent.

cluding plantar responses. The patient improved over 2 weeks and was discharged with persisting mild dysarthria.

Case 13.—An 81-year-old hypertensive man was admitted for sudden dysarthria. On admission, his blood pressure was 180/80 mm Hg. Bilateral facial paresis was present. He could not close his eyes voluntarily, while corneal reflex was normal. The jaw reflex was brisk. No sensory deficit was noted over the face. The soft palate was paralyzed, and the gag reflex was abolished. The patient was unable to speak, to swallow, to chew, or to move his tongue. The rest of the neurologic examination showed a right hemiplegia with right-sided Babinski's sign. The patient improved over 5 weeks and was left with mild paresis of the right hand and dysarthria.

RESULTS

CT and MRI Findings (Table 1)

In group 1 (Fig 1), bilateral small, deep infarcts were found in four patients, involving the rostral part of the posterior limb of the internal capsule in patients 1 and 2, and the corona radiata in patients 5 and 6. A bilateral superficial middle cerebral artery territory infarct involving the opercular region was found in patient 3. A superficial middle cerebral artery territory infarct was associated with a contralateral capsulolenticular hemorrhage in patient 7. In patient 4, multiple periventricular small, deep infarcts were found. The old previously asymptomatic lesion was a deep infarct in five patients (patients 1, 2, 4, 5, and 6) and was a superficial middle cerebral artery territory infarct in two patients (patients 3 and 7).

In group 2 (Fig 2), bilateral deep infarcts were found in three patients, involving the corona radiata in patient 8, the rostral part of the posterior limb of the internal capsule in patient 9, and the genu of the internal capsule in patient 12. A superficial middle cerebral artery infarct involving the opercular region was associated with a contralateral deep infarct in patients 10, 11, and 13.

Clinical Features (Table 2)

There were seven men and six women ranging in age from 40 to 81 years old. Five patients experienced an isolated complete faciopharyngoglossomasticatory palsy (patients 1, 6, 7, 11, and 12). Three patients experienced a faciopharyngoglossomasticatory palsy with hemiparesis (patients 3, 10, and 13). In five patients (patients 2, 4, 5, 8, and 9), the pseudobulbar palsy was only partial. One patient had involuntary laughing and crying (patient 3). None had trismus.

Neuropsychologic examination[10] was normal except in patient 2. This patient was unable to realize Luria conflicting tasks and sequential rhythms. The results of Raven PM 38 were abnormal (14 points). Recognition of face was impaired (15/27, Benton). Visual learning was severely impaired (23 of 40, learning of faces; 8 of 40, learning of countries).

The most common vascular concomitant was hypertension (11 of 13) (Table 3). Symptomatic heart disease was present in three patients, diabetes mellitus in three patients, and hypercholesterolemia in four patients. Extracranial Doppler ultrasound results showed internal carotid artery occlusion in two patients and was unremarkable in all other patients. Transcranial Doppler ultrasound results showed no detection of the right anterior cerebral artery in one patient and was normal in six patients.

COMMENT

Pseudobulbar or suprabulbar palsy developed acutely in all our patients. Although some patients have been presented,[11-17] the acute onset of pseudobulbar palsy is considered unusual. This acute onset may be explained by an acute damage to corticonuclear fibers on one side when contralateral corticonuclear fibers have been previously interrupted. This previous lesion may have been symptomatic (group 1) or asymptomatic (group 2). Actually, unilateral stroke limited to corticonuclear pathways may be asymptomatic if it is small and respects the corticospinal tract. When symptomatic, unilateral corticonuclear pathway damage usually produces only lower facial weakness. This may be explained by the classic notion that corticonuclear pathways project bilaterally toward cranial nerve nuclei, except to the lower facial nucleus.

Supranuclear innervation of the tongue may also be mainly unilateral. After his first stroke, patient 5 had a supranuclear palsy of the right XIIth cranial nerve associated with a small infarct in the medial part of the left corona radiata. Some other cases of deep lesions producing a supranuclear palsy of the XIIth cranial nerve have been described previously,[18-21] and 10% of small, deep infarcts of the carotid artery territory may have contralateral tongue paresis.[21] More uncommonly, patients with unilateral palatal palsy[22] or unilateral vocal cord palsy[23] have been described in association with a deep infarct involving corticonuclear pathways in the internal capsule or corona radiata. Trapezius or sternocleidomastoid muscle palsy has rarely been reported in pseudobulbar palsy.[24]

Three of our patients had XIth cranial nerve palsy, which was bilateral in two (patients 3 and 7) and unilateral in one (patient 8). In both patients with bilateral XIth cranial nerve palsy, one had superficial middle cerebral artery territory infarction on both sides and the other had a superficial middle cerebral artery territory infarct associated with a contralateral capsulolenticular hemorrhage. In the patient with unilateral left supranuclear XIth cranial nerve palsy, MRI showed a deep infarct in the posterior part of the right corona radiata near the lateral ventricule and a small, deep infarct in the medial part of the contralateral corona radiata. The supranuclear innervation to the XIth cranial nerve is controversial. Either a direct uncrossed innervation[25] or a double decussation[26] have been suggested. Patients with hemiplegia due to hemispheric lesions had weakness of the sternocleidomastoid muscle ipsilateral to the lesion,[27] which suggested that this muscle is controlled by the ipsilateral hemisphere. This is in contradiction with reports of presumed unilateral opercular syndrome with unilateral contralateral pseudobulbar palsy of the fifth, seventh, and ninth through XIIth cranial nerves.[24,28-31] However, none of these patients underwent autopsy, CT, or MRI studies. Rousseaux et al[32] have described a patient with unilateral facial, masseter, palatal, and pharyngeal palsy induced by a small infarct in the genu of the contralateral internal capsule. However the authors did not find sternocleidomastoid or trapezius muscle weakness, suggesting that the supranuclear pathway of the XIth cranial nerve was either spared or came from the ipsilateral hemisphere.

Five patients experienced an isolated faciopharyngoglossomasticatory palsy that has been mainly reported in bilateral frontal operculum lesions.[6,33-39] However, none of our patients had a bilateral operculum lesion on CT or MRI. In three patients, a bilateral deep infarct was found (patients 1, 6, and 12). A superficial middle cerebral artery infarct was associated with a contralateral deep infarct in one patient (patient 11) and with a contralateral lenticulocapsular hemorrhage in another patient (patient 7). A sixth patient experienced a faciopharyngoglossomasticatory palsy with unilateral mild hemiparesis in relation to a superficial middle cerebral artery infarct involving the operculum and contralateral deep infarct (patient 10). Bilateral faciopharyngoglossomasticatory palsy has rarely been reported with nonopercular lesions. In 1884, Raymond and Artaud[40] presented a 67-year-old man with faciopharyngoglossomasticatory palsy and mental impairment; a bilateral hemorrhage involved the lateral part of both lenticular nuclei and the anterior arm of both internal capsules. In 1898, Tournier[41] described a patient with bilateral faciopharyngoglossomasticatory palsy associated with trismus and left arm monoplegia; at autopsy, he found a right opercular infarct and two left deep infarcts involving the superomedial part of the thalamus and the lenticular nucleus. In 1979, Fisher[42] presented a patient (case 5) with faciopharyngoglossomasticatory palsy and mild right hemiparesis; at autopsy, he found bilateral deep infarcts situated in the genu of the internal capsules. In 1985, Leys et al[14] described a patient with bilateral faciopharyngoglossomasticatory palsy due to an infarct in the upper part of the genu of the internal capsule on both sides on CT. In 1988, Starkstein et al[43] presented a patient with bilateral faciopharyngoglossomasticatory palsy, aphemia, left hemiparesis, and left hemineglect; at autopsy, they found a unilateral infarct involving the right insula, while the left hemisphere, the brain stem, and the cerebellum appeared normal. These previous reports and our findings confirm that bilateral faciopharyngoglossomasticatory palsy may result from bilateral frontal operculum involvement, but they also suggest that bilateral damage to corticonuclear pathways sparing pyramidal pathways may not be uncommon.

Six patients had a pseudobulbar palsy produced by bilateral deep infarcts. However, only one had neuropsychologic impairment (patient 2) and none had forced laughing and crying, which have been usually reported in chronic pseudobulbar palsy from striatocapsular involvement. On the other hand, involuntary laughing and crying was present in one patient who had bilateral cortical infarcts (patient 3). Involuntary laughing and crying is uncommon in the chronic form of pseudobulbar palsy due to cortical lesions.[44] Involuntary laughing and crying is supposed to result from decreased inhibition over centers controlling emotional facial movements.[45] Centers and pathways involved in laughing and crying are yet unknown. Yarnell[46] postulated that involuntary laughing and crying in right-handed patients corresponded to a lesion interrupting connections between the right middle cerebral artery territory and the left pons. Recently, a patient with isolated involuntary laughing and crying induced by a small brainstem vascular malformation was described.[47] Lack of pseudobulbar sign suggested that corticonuclear tract lesions are not necessary to produce these symptoms.

The most prominent vascular concomitant was hypertension in our patients. Three patients (patients 1, 7, and 12) had a potential cardiac source of embolism. These three patients were also hypertensive, one had hypercholesterolemia (patient 1) and one was a smoker. Among these three patients, two had bilateral small, deep infarcts (patients 1 and 12) and one had a superficial middle cerebral artery territory infarct associated with a contralateral lenticulocapsular hemorrhage. Extracranial vascular abnormalities were found in two patients (patients 7 and 10) who were also hypertensive. Therefore, acute pseudobulbar palsy may identify a subgroup of patients in whom large-artery disease and cardioembolism are an unlikely cause for stroke.

Our findings suggest that acute pseudobulbar palsy, either with or without prior stroke, may be more common than what the recent literature suggests. It may be associated with infarct or hemorrhage involving the frontal opercular region or the corticonuclear pathways in both cerebral hemispheres, but largely sparing the corticospinal pathways.

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References

1. Lépine R. Note sur la paralysie glosso-labiée cérébrale à forme pseudo-bulbaire. *Rev Mens Med Chir.* 1877;1:909-922.

2. Magnus A. Fall von Aufhebung des Willenseinflusses auf einige Hirnnerven. *Müller Arch.* 1837:258-266.

3. Jolly F. Ueber multiple Hirnsklerose. *Arch Psychiatr Nerv.* 1872:711-730.

4. Joffroy A. Sur un cas de paralysie labio-glosso-laryngée à forme apoplectique d'origine bulbaire. *Gaz Med Paris.* 1872:494-496.

5. Thurel R. *Les Pseudobulbaires: Etude Clinique et Anatomopathologique.* Paris, France: Jouve; 1929. Thesis.

6. Foix C, Chavany JA, Marie J. Diplégie facio-linguo-masticatrice d'origine cortico sous-corticale. *Rev Neurol.* 1926;33:214-219.

7. Langworthy OR, Hesser FH. Syndrome of pseudobulbar palsy: an anatomic and physiologic analysis. *Arch Intern Med.* 1940;65:106-121.

8. Loeb C, Gandolfo C, Caponnetto C, Del Sette M. Pseudobulbar palsy: a clinical computed tomography study. *Eur Neurol.* 1990;30:42-46.

9. Bogousslavsky J, Van Melle G, Regli F. The Lausanne stroke registry: analysis of 1000 consecutive patients with first stroke. *Stroke.* 1988;19:1083-1092.

10. Assal G. Examen fonctionnel des zones cérébrales du langage: de l'examen au syndrome anatomo-clinique. *Med Hyg.* 1980;38:3358-3370.

11. Buge A, Escourolle R, Hauw JJ, Rancurel G, Gray F, Tempier P. Syndrome pseudobulbaire aigu par infarctus bilatéral limité du territoire des artères choroïdiennes antérieures. *Rev Neurol.* 1979;135:313-318.

12. Cambier J, Viader F, Paquelin F, Poullot B, Pariser P. Dyspnée laryngée périodique au cours d'un syndrome bi-operculaire. *Rev Neurol.* 1983;139:531-533.

13. Villa G, Caltagirone C. Speech suppression without aphasia after bilateral perisylvian softenings (bilateral rolandic operculum damage). *Ital J Neurol Sci.* 1984;5:77-83.

14. Leys D, Lejeune JP, Bourgeois P, Blond S, Petit H. Syndrome pseudo-bulbaire aigu: infarctus bilateral de la jonction capsule interne-corona radiata. *Rev Neurol.* 1985;141:814-818.

15. Helgason C, Wilbur A, Weiss A, Redmond KJ, Kingsbury NA. Acute pseudobulbar mutism due to discrete bilateral capsular infarction in the territory of the anterior choroidal artery. *Brain.* 1988;111:507-524.

16. Boulay G. Des pseudo-paralysies bulbaires. *Gaz Med Paris.* 1891:793-800.

17. Dejérine J. La paralysie pseudo-bulbaire. *Rev Gen Clin Ther.* 1914;28:406-408.

18. Fisher CM, Curry HB. Pure hemiplegia of vascular origin. *Arch Neurol.* 1965;13:30-44.

19. Bogousslavsky J, Regli F. Hémiparésie avec atteinte linguale: hèmatome du genou de la capsule interne. *Rev Neurol.* 1984;140:587-590.

20. Bogousslavsky J, Regli F. Capsular genu syndrome. *Neurology.* 1990;10:1499-1502.

21. Ghika J, Bogousslavsky J, Regli F. Infarcts in the territory of the deep perforators from the carotid system. *Neurology.* 1989;39:507-512.

22. Iwata M. Unilateral palatal paralysis caused by lesion in the corticobulbar tract. *Arch Neurol.* 1984;41:782-784.

23. Garel J, Dor L. Du centre cortical moteur laryngé et du trajet intra-cérébral des fibres qui en émanent. *Ann Mal Oreil Larynx.* 1890;16:209-235.

24. Schott B, Boulliat G, Cotte L, Vauterin C. Le syndrome operculaire bilatéral et unilatéral. *Lyon Med.* 1961;261:365-377.

25. Balagura S, Katz RG. Undecussated innervation to the sternomastoid muscle: a reinstatement. *Ann Neurol.* 1980;7:84-85.

26. Geschwind N. Nature of the decussated innervation of the sternomastoid muscle. *Ann Neurol.* 1981;10:495.

27. Mastaglia FL, Knezevic W, Thompson PD. Weakness of head turning in hemiplegia: a quantitative study. *J Neurol Neurosurg Psychiatry.* 1986;49:195-197.

28. Alajouanine T, Boudin G, Pertuiset B, Pèpin B. Le syndrome unilatéral de l'opercule rolandique avec atteinte controlatérale du territoire des V, VII, IX, X, XI, XII^{e} nerfs crâniens. *Rev Neurol.* 1959;101:168-171.

29. Pertuiset B, Perrier F. Le syndrome unilatéral (rolandique inférieur) d'origine vasculaire. *Rev Neurol.* 1960;103:63-64.

30. Boudin G, Pèpin B, Wiart JP. Le syndrome operculaire unilatéral d'origine vasculaire. *Rev Neurol.* 1960;103:65.

31. Rebucci GG, Gambetti P, Bottazzi G. Le syndrome unilatéral de l'opercule rolandique: à propos de trois observations cliniques. *Acta Neurol Psychiatr Belg.* 1964;64:1267-1278.

32. Rousseaux M, Lesoin F, Quint S. Unilateral pseudobulbar syndrome with limited capsulothalamic infarction. *Eur Neurol.* 1987;27:227-230.

33. Foix C, Chavany JA. Diplégies faciales (facio-linguo-pharyngo-masticatrices), d'origine corticale, avec quelques considérations sur les paralysies pseudo-bulbaires et la localisation des centres corticaux de l'extrémité céphalique. *Ann Med.* 1926;20:480-498.

34. Alajouanine T, Thurel R. La diplégie faciale cérébrale, forme corticale de la paralysie pseudobulbaire (contribution à l'étude de la dissociation des activités volontaires et réflexes). *Rev Neurol.* 1933;40:441-458.

35. Schwob RA, Gruner J, Mamo H. Trois cas de trismus cérébral par lésions cortico-sous-corticales. *Rev Neurol.* 1956;94:410-411.

36. Château R, Fau R, Groslambert R, Perret J, Boucharlat J, Châtelain R. A propos de trois observations de diplégie linguo-facio-masticatrice d'origine corticale: la forme de l'adulte et celle de l'enfant. *Rev Neurol.* 1966;114:390-395.

37. Ferrari G, Boninsegna C, Beltramello A. Foix-Chavany syndrome: CT study and clinical report of three patients. *Neuroradiology.* 1979;18:41-42.

38. Mariani C, Spinnler H, Sterzi R, Vallar G. Bilateral perisylvian softenings: bilateral anterior opercular syndrome (Foix-Chavany-Marie syndrome). *J Neurol.* 1980;223:269-284.

39. Mao CC, Coul BM, Golper LAC, Rau MT. Anterior operculum syndrome. *Neurology.* 1989;39:1169-1172.

40. Raymond F, Artaud G. Contribution à l'étude des localisations cérébrales (trajet intracérébral de l'hypoglosse). *Arch Neurol.* 1884;7:145-172.

41. Tournier C. Double hémiplégie: trismus persistant: syndrome de paralysie glosso-labio-faciale pseudo-bulbaire d'origine cérébrale: ophtalmoplégie ne portant que sur les mouvements volontaires avec conservation des mouvements réflexes. *Rev Med.* 1898;18:671-679.

42. Fisher CM. Capsular infarcts: the underlying vascular lesions. *Arch Neurol.* 1979;36:65-73.

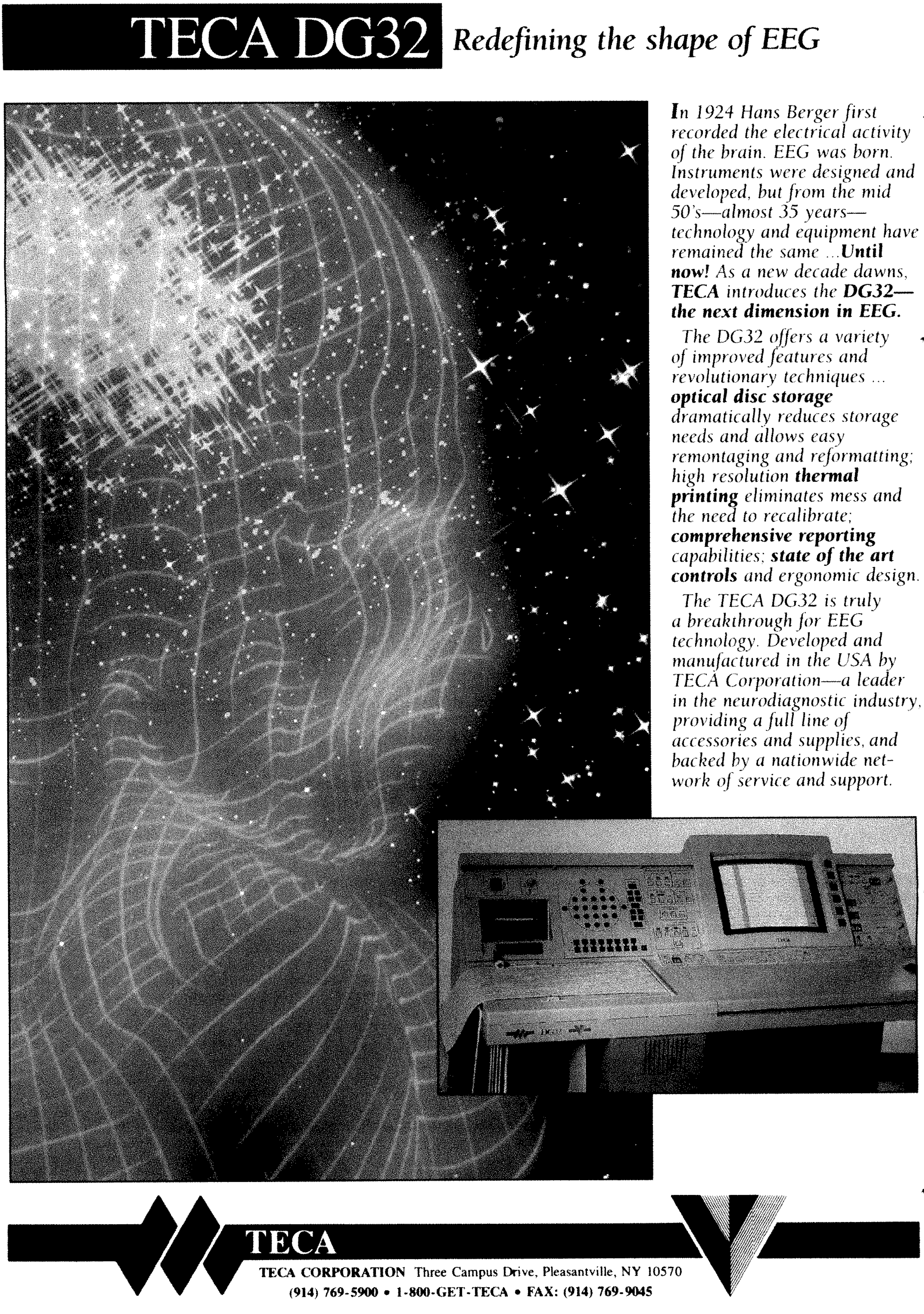
43. Starkstein SE, Berthier M, Leiguarda R. Bilateral opercular syndrome and crossed aphemia due to a right insular lesion: a clinicopathological study. *Brain Lang.* 1988;34:253-261.

44. Bruyn GW, Gathier JC. The operculum syndrome. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology.* Amsterdam, the Netherlands: North-Holland; 1969;2:776-783.

45. Poeck K. Pathophysiology of emotional disorders associated with brain damage. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology.* Amsterdam, the Netherlands: North-Holland; 1969;3:355-367.

46. Yarnell PR. Pathological crying localization. *Ann Neurol.* 1987;22:133-134.

47. Asfora WT, De Salles AAF, Abe M, Kjellberg RN. Is the syndrome of pathological laughing and crying a manifestation of pseudobulbar palsy? *J Neurol Neurosurg Psychiatry.* 1989;52:523-525.



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• Stuttering is a poorly understood communication disorder with a 1% global prevalence. Recently, there has been a resurgence of interest in a neurogenic origin for the disorder, although no research has established clear neurological differences between "developmental" (stuttering onset in childhood) stutterers and nonstutterers. We have used xenon 133 single-photon emission computed tomography to study regional cerebral blood flow (rCBF) in 20 stutterers. Analysis revealed global, absolute flow reductions. Relative flow asymmetries (left < right) were identified in three hemispheric regions: anterior cingulate and superior and middle temporal gyri. Milder changes were found in the left inferior frontal gyrus. Stutterers had rCBF values below median for either anterior cingulate or middle temporal gyri. With one exception, severe stutterers had rCBF values below median for the anterior cingulate gyrus. All stutterers with rCBF values above median in the cingulate gyrus had rCBF values below median in the middle temporal gyrus, and severity of their disorder was either mild or moderate. Our findings suggest that stuttering is a neurogenic disorder involving recognized cortical regions of speech-motor control.

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Stuttering is a disruption in the fluency of verbal expression characterized by involuntary audible or silent repetitions or prolongations in the utterance of short speech elements, eg, sounds, syllables, and words of one syllable.[1] According to Shames,[2] nearly 1% of American adults and children stutter. For one person in 300, stuttering constitutes a severe communication disorder.

Both psychogenic and neurogenic origins have been proposed for stuttering. In the 19th century, a number of authorities offered neurological theories of stuttering (as reviewed by Van Riper[3]). Kussmaul[4] viewed stuttering as an aphasia that produced a syllabic dysarthria characterized by a lack of coordination of voice, respiration, and articulation. Based on a series of case studies of aphasic (acquired) stuttering, Gutzmann[5] considered stuttering a result of a deficiency in the cerebral cortex that impaired syllabic coordination. In the 1980s, we have seen a reemergence of interest in stuttering secondary to nervous system damage, especially "acquired" stuttering subsequent to head trauma and stroke.[6] There remains, however, no conclusive evidence of a neurogenic basis for developmental (onset in childhood) stuttering.[7]

A number of current theories represent experimentally based elaborations of these early speculations, and they alternatively view stuttering as a sequencing and timing disorder,[8] as a temporal programming disorder,[9] as a prosodic disorder,[10] and as a cognitive-linguistic disorder.[11] In attempting to reconcile divergent stuttering theories, as well as experimental results, heterogeneous models have been proposed.[12] Recent evidence from studies of speech-motor control in stutterers provide some evidence that severe stutterers differ from mild and moderate stutterers along the parameters that could coincide with differences in underlying neuropathophysiologic causes.[13]

Alterations in brain function, as reflected by cerebral blood flow or metabolism, might provide a sensitive tool for elucidation of neurologic function in stuttering and for differentiation of clinical subgroups. Wood et al[14] investigated patterns of regional cerebral blood flow (rCBF) in two stutterers. Subjects read aloud while receiving and not receiving haloperidol medication. In both cases, stutterers showed reduced cortical blood flow to Broca's area compared with the homologous area of the right hemisphere while not receiving haloperidol. When the stuttering subjects were fluent (when taking haloperidol medication), greater flow was observed in the left hemisphere compared with the right.

The present article reports the rCBF patterns in 20 adult developmental stutterers who were studied using xenon 133 single-photon emission computed tomography (SPECT). The purpose of the study was to determine whether rCBF in stutterers differed from that in normal subjects and whether rCBF differences were related to differences in stuttering severity.

SUBJECTS AND METHODS

Subjects

Twenty adult stutterers (19 male and one female) provided informed consent to participate in this study according to the guidelines of our Institutional Review Board. Age of subjects ranged from 24 to 59 years (mean age, 37 years). Nine subjects began stuttering in early childhood (before age 5 years); nine subjects began in later childhood (between 5 and 12 years of age); and two subjects reported postpuberty onset. Twelve subjects reported a family history of stuttering. These 12 included one set of twins and one set of brothers. Not counting these siblings, eight subjects had a positive family history of stuttering. Two subjects were left-handed and 18 were right-handed. All subjects had received some form of speech therapy, ranging from a few ses-

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sions to over 7 years of therapy. Five subjects were receiving speech therapy when studied.

Seventy-eight age-matched subjects selected from 97 previously described laboratory subjects[15] were used for comparison with the 20 stutterers. Laboratory control subjects had an average age of 33 years (range, 20 to 59 years), and they were screened by history for significant neurologic involvement including transient ischemic attack, stroke, head trauma, diabetes, hypertension, and psychiatric disorders. They were not taking any psychoactive medication. Absolute rCBF values in stutterers were compared with those in a gender-matched subgroup of 43 subjects with a mean age of 40 years (SD, 15 years). Flow ratios, which are not gender-sensitive, were examined for all 78 control subjects.

Mean Absolute Regional Cerebral Blood Flow (rCBF) Values in 78 Age-Matched Normal Control Subjects and 20 Stutterers

Region of Interest	Mean (SD) Absolute rCBF, mL/min/100g Normal Subjects	 Stutterers
L superior frontal	72 (15)	52 (10)
R superior frontal	74 (15)	55 (12)
L anterior cingulate	76 (16)	60 (13)
R anterior cingulate	77 (16)	64 (15)
L middle frontal	65 (13)	49 (12)
R middle frontal	68 (13)	51 (11)
L inferior frontal	73 (14)	55 (13)
R inferior frontal	78 (14)	60 (11)
L precentral/postcentral	76 (14)	59 (13)
R precentral/postcentral	82 (15)	62 (12)
L superior temporal	71 (14)	59 (14)
R superior temporal	76 (14)	64 (13)
L middle temporal	60 (13)	50 (13)
R middle temporal	66 (12)	56 (13)
L inferior temporal	47 (11)	37 (11)
R inferior temporal	56 (10)	45 (13)
L occipital	60 (11)	52 (15)
R occipital	68 (12)	57 (17)
L precuneus	76 (15)	64 (11)
R precuneus	87 (17)	69 (12)

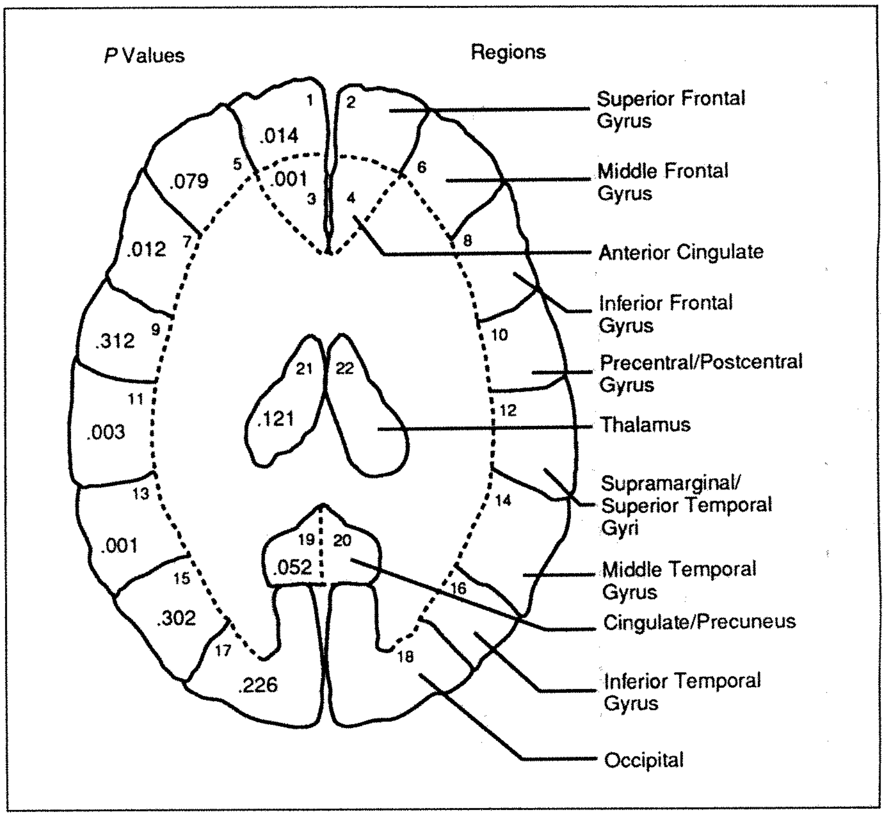

Fig 1.—Relative flow asymmetries: regions of interest and *P* values. Points are mean ± 1 SD.

Fluency Evaluation

For all 20 stutterers, multiple fluency measures were analyzed using clinical behavioral assessments.[16,17] Percent dysfluency, duration of longest blocks, and secondary symptoms were used in global ratings of severity. When these three measures were considered, 10 of the 20 stutterers were classified as severe, four as moderate, and six as mild.

Magnetic Resonance Imaging

Magnetic resonance imaging scans were unrevealing for 19 of 20 stutterers. One subject's left cervical and intracavernous internal carotid artery could not be visualized. Possible explanations include occlusion or dissection or severe hypoplasia.

rCBF

The rCBF was measured quantitatively in three tomographic cross sections using the tomograph (Tomomatic 64 SPECT, Medimatic A/S, Copenhagen, Denmark), as described by Stokely et al.[18] This tomograph consists of four detector arrays, each containing 16 sodium iodide (thallium) scintillation crystals mounted in a hollow-square configuration that rotates about the subject's head at 6 rpm. Special focused collimators define three transverse tomographic sections with centers 4 cm apart. Xenon 133 was administered in an air/oxygen mixture (10 mCi/L) by inhalation during the first minute of a 4-minute wash-in/wash-out procedure. The subject breathes room air during the remaining 3 minutes of the study. During the tomographic measurement of the cerebral transit of xenon 133, activity in the lung is monitored by a scintillation probe placed over the right upper quadrant of the subject's chest. This lung activity is assumed to be proportional to the arterial blood concentration of xenon 133 arriving at the brain. Three tomographic cross sections are generated by filtered back-projection with attenuation correction, according to the method of Kay and Keyes.[19] The rCBF is calculated according to the double-integral method.[20-22] The lung curve is used as the input function to the Kanno-Lassen algorithm to compensate for delivery of tracer by inhalation rather than by direct injection into the internal carotid artery.[23] The rCBF images are displayed in a 64 × 64 matrix, employing a 16-shade scale adjusted to range from zero flow to maximum flow. Transverse resolution is 1.7 cm, and axial resolution is 1.9 cm.

Subjects were positioned in the tomograph using a face-marking template so that cross sections were obtained 2, 6, and 10 cm above and parallel to the canthomeatal line. They were studied in the supine position, with eyes open, and ears unplugged in a dimly lit room with background noise originating primarily from instrument cooling fans. Subjects breathed through a fitted mouthpiece while their nostrils were occluded by a spring clamp. An approximately 2-minute adaptation time was allowed prior to initiating the study. Each subject was asked to take a deep breath at the beginning of the study, after which no further communication occurred. These procedures and values in

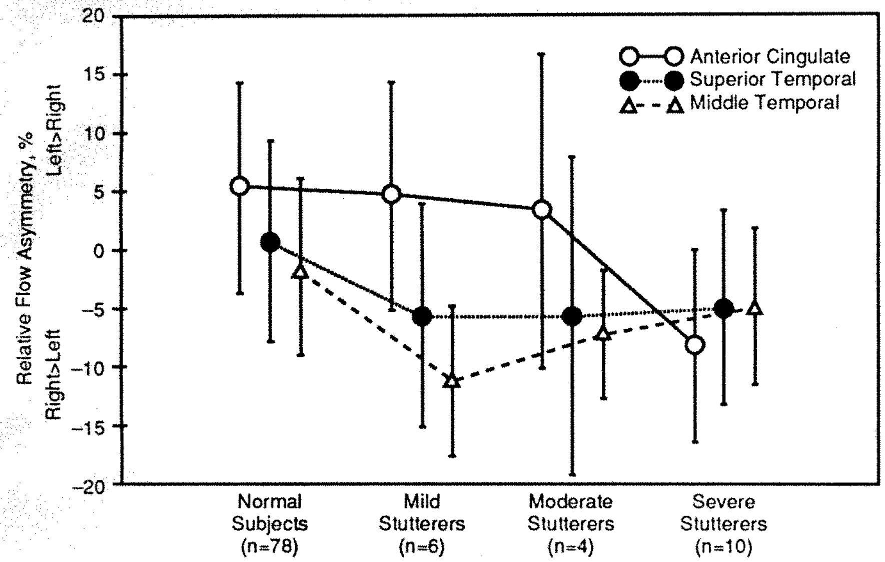

Fig 2.—Relative regional cerebral flow asymmetries by severity of stuttering.

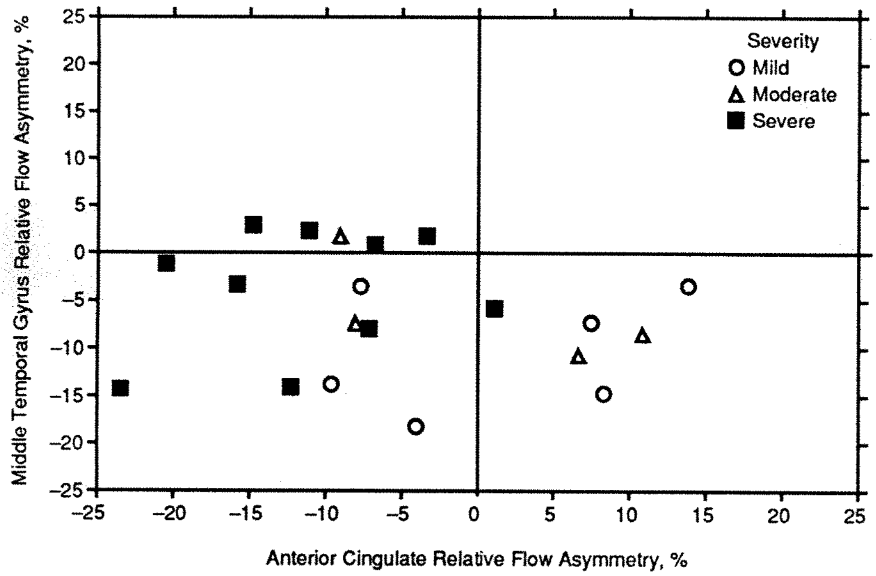

Fig 3.—Stuttering severity vs relative flow asymmetry of regional cerebral blood flow. All relative asymmetries are relative to median values in normal control subjects.

normal subjects, reproducibility, intersubject variability, and asymmetries have been described in detail by Devous et al.[15]

Quantitative rCBF Analyses

The rCBF images were transferred from the V77 computer (Univac) to a PE 3241 computer (Perkin-Elmer). This system, coupled to a graphics tablet (Talos Cybergraph) and a 512 × 512 × 8-bit frame buffer (Genisco GCT-3000) with a color monitor (Tektronix 670-A-1), is used with an interactive graphics software package to obtain rCBF values from images. Stokely et al[24] describe this analysis scheme in detail. Briefly, rCBF images are scaled, rotated, and translated to match a predefined standard brain outline that includes graphic overlay of regions of interest (ROIs) determined from a digitized atlas of CT and gross pathological specimens (individual CT data are not used). The only operator interface required is the identification of the positions of major and minor axes on an ellipse that is fit to the outer boundary of the rCBF image. Regional flows and their SDs are obtained from frontal, parietal, superotemporal, occipital, and central gray matter, as well as white matter and both hemispheres, using the section 6 cm above the canthomeatal line. Inferotemporal and cerebellar flows are obtained from the section 2 cm above the canthomeatal line. The automatic fitting routine produces standard scaling and reproducible ROIs so that operator intervention has a minimal effect on results. All visual and digitized flow data in the current study were generated from section two, 6 cm above the canthomeatal line, as this section best represents major cortical ROIs.

Flow values from ROI analyses were then normalized by dividing each region by the average flow to that hemisphere for both patients and 78 normal control subjects. Asymmetry was then calculated as (left ROI ratio − right ROI ratio) for both groups. Differences between stutterers and control subjects were examined by computing the asymmetry difference for the study subjects relative to the median value for control subjects for each region (referred to subsequently as *relative flow asymmetry*).

Statistical Analysis

Differences in absolute flow values between groups in 20 cortical ROIs were examined by sign test. Relative rCBF asymmetries were statistically corrected for multiple measures to determine if there were focal rCBF reductions in stuttering using multiple measurement t tests for small sample size. To achieve an experiment-wise significance of $P < .05$, the individual measure significance cutoff was set at $P < .005$.

RESULTS

The rCBF was globally reduced in stutterers (Table) compared with that in both age- and gender-matched normal control subjects (mean flow in stutterers below mean flow in normal control subjects for 20 of 20 atlas-derived cortical ROIs; sign test, $P < .0001$). Significant relative flow asymmetry (left < right) was found for the anterior cingulate (t[96] = 3.2; $P < .005$) and superior (t[96] = 2.8; $P < .005$) and middle temporal gyri (t[96] = 3.1; $P < .005$). Milder asymmetry was seen in the inferior frontal gyrus (t[96] = 2.3; $P < .01$). Results for all 10 asymmetry flow measures are shown in Fig 1.

Mean relative rCBF asymmetry in anterior cingulate and superior and middle temporal gyri for normal control subjects, and for mild, moderate, and severe stutterers is shown in Fig 2. Flow asymmetries are present in the superior and middle temporal gyri for all stutterers. While there is less asymmetry in the middle temporal gyrus for severe stutterers compared with mild and moderate subjects, this difference is not significant for group averaged data. Group average flow asymmetries in the anterior cingulate gyrus are limited to the severe stuttering group. The relationship of individual flow asymmetries to global perceptual stuttering severity is illustrated in Fig 3. All stutterers had flow asymmetry below median (left reduced relative to right) for either anterior cingulate or middle temporal gyri. All but one severe stutterer had below median value for the anterior cingulate gyrus. All stutterers with values above median in cingulate had values below median in the middle temporal gyrus and they were either mild or moderate stutterers.

COMMENT

An association between dysfluency in stuttering and cortical dysfunction in the left cingulate and left inferior frontal gyrus is consistent with classic anatomoclinical principles of speech-motor control. Motor initiation deficits have been localized to the mesiofrontal cortex in the region of the cingulate or supplementary motor area.[25] Motor programming for speech has been localized to the left perisylvian (inferior frontal) cortex.

But what of the finding of left temporal lobe hypoperfusion, especially in mild to moderate stutterers? The question of a relationship between stuttering and temporal lobe dysfunction has a long history. Auditory tests, including auditory electrophysiologic tests, have performed two functions in stuttering research: (1) as a measure of cerebral dominance for language and (2) in the search for abnormalities of the auditory feedback mechanism subserving speech production.[7] Unfortunately, while individual findings have often pointed to temporal lobe dysfunction,[26] or to auditory brainstem dysfunction,[27,28] the heterogeneity in stuttering often precluded significant results. Rosenfield and Jerger[7] acknowledged the conflicting evidence, but they did not discard persistent findings implicating the central auditory system. Our data support their contention that there may be a link to the temporal lobe in at least a subgroup of stutterers.

Further evidence for a role of temporal lobe involvement in speech-motor dysfunction was reported in three separate rCBF studies of children labeled dysphasic.[29-31] Hypoperfusion (and hence low metabolic activity) in cortical regions similar to those found herein was reported in all three studies. In a study by Denays et al,[29] two children with an expressive impairment demonstrated hypoperfusion in the left inferior frontal convolution, involving Broca's area. Billard et al[30] reported posterotemporal flow deficits in patients with primarily expressive deficits. Lou et al[31] reported frontal lobe and perisylvian hypoperfusion in their three patients with verbal dyspraxia. The similarity of these identified lesion sites and those reported herein to those expected in a known disorder of language like acquired aphasia reminds us of Kussmaul's aphasia/stuttering hypothesis, in which stuttering was described as an aphasia that produced a syllabic dysarthria characterized by a lack of coordination of voice, respiration, and articulation.

While we are far from unraveling the neuropathophysiologic origin of stuttering, these data provide intriguing preliminary evidence for cortical dysfunction in stutterers related to reduced and asymmetric left frontal and temporal perfusion. This study should be considered an exploratory data analysis. We are undertaking confirmatory research in a larger group of stutterers.

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References

1. Wingate ME. A standard definition of stuttering. *J Speech Hear Disord.* 1964;29:484-489.
2. Shames G. Disorders of fluency. In: Shames G, Wiig E, eds. *Human Communication Disorders (An Introduction).* 2nd ed. Columbus, Ohio: Charles Merril; 1986.
3. Van Riper C. *The Nature of Stuttering.* 2nd ed. Englewood Cliffs, NJ: Prentice-Hall International Inc; 1982:323-327.
4. Kussmaul A. *Die Storungen der Sprache.* In: Ziemssen HV, ed. *Cyclopaedia Medica,* 1877. Reported by: Klingbeil GM. The historical background of the modern speech clinic. *J Speech Disord.* 4:115-132 and Van Riper C. *The Nature of Stuttering.* 2nd ed. Englewood Cliffs, NJ: Prentice-Hall International Inc; 1982.
5. Gutzmann H. *Das Stottern.* Frankfurt am Main, Germany: J Rosenheim; 1898.
6. Rosenbek JC. Stuttering secondary to nervous system damage. In: Curlee RF, Perkins WF, eds. *Nature and Treatment of Stuttering: New Directions.* San Diego, Calif: College Hill Press; 1984.
7. Rosenfield DB, Jerger J. Stuttering and auditory function. In: Curlee RF, Perkins WH, eds. *Nature and Treatment of Stuttering.* San Diego, Calif: College Hill Press; 1984:73-87.
8. MacKay DG, MacDonald MC. Stuttering as a sequencing and timing disorder. In: Curlee RF, Perkins WH, eds. *Nature and Treatment of Stuttering: New Directions,* San Diego, Calif: College Hill Press; 1984.
9. Kent RD. Stuttering as a temporal programming disorder. In: Curlee RF, Perkins WH, eds. *Nature and Treatment of Stuttering: New Directions.* San Diego, Calif: College Hill Press; 1984.
10. Wingate M. Stuttering as a prosodic disorder. In: Curlee RF, Perkins WH, eds. *Nature and Treatment of Stuttering: New Directions.* San Diego, Calif: College Hill Press; 1984.
11. Hamre CE. Stuttering as a cognitive-linguistic disorder. In: Curlee RF, Perkins WH, eds. *Nature and Treatment of Stuttering: New Directions.* San Diego, Calif: College Hill Press; 1984.
12. Clutter MH, Freeman FJ. Stuttering: six blind men revisited. *J Fluency Disord.* 1984;9:89-92.
13. Watson BC, Alfonso P. Foreperiod and stuttering severity effects on acoustic laryngeal reaction time. *J Fluency Disord.* 1983;8:183-205.
14. Wood F, Stump D, McKeehan A, Sheldon S, Proctor J. Patterns of regional cerebral blood flow during attempted reading aloud by stutterers both on and off haloperidol medication: evidence for inadequate left frontal activation during stuttering. *Brain Lang.* 1980;9:141-144.
15. Devous MD, Stokely EM, Chehabi HH, Bonte FJ. Normal distribution of regional cerebral blood flow measured by dynamic single-photon emission tomography. *J Cereb Blood Flow Metab.* 1986;6:95-104.
16. Riley G. *Stuttering Severity Instruments for Children and Adults. (revised).* Tigerd, Ore: CC Publications; 1980.
17. Ryan B. *Programmed Therapy for Stuttering in Children and Adults.* Springfield, Ill: Charles C Thomas Publisher; 1974.
18. Stokely EM, Sveindsdottir E, Lassen NA, et al. A single-photon dynamic computer assisted tomograph (DCAT) for imaging brain function in multiple cross sections. *J Comput Assist Tomogr.* 1980;4:230-240.
19. Kay DB, Keyes JW Jr. First order correction for absorption and resolution compensation in radionuclide Fourier tomography. *J Nucl Med.* 1975;16:540-541.
20. Kanno I, Lassen NA. Two methods of calculating regional cerebral blood flow from emission computed tomography of inert gas concentrations. *J Comput Assist Tomogr.* 1975;3:71-76.
21. Celsis P, Goldman T, Henrichsen L, Lassen NA. A method for calculating regional cerebral blood flow from emission computerized tomography of inert gas concentrations. *J Comput Assist Tomogr.* 1981;5:641-645.
22. Smith GT, Stokely EM, Lewis MH, et al. An error analysis of the double integral method of calculating brain blood perfusion from inert gas clearance data. *J Cereb Blood Flow Metab.* 1985;4:61-67.
23. Devous MD, Stokely EM, Bonte FJ. Quantitative imaging of regional cerebral blood flow in man by dynamic single-photon tomography. In Homan BL, ed. *Radionuclide Imaging of the Brain.* New York, NY: Churchill-Livingstone Inc, 1985:135-162.
24. Stokely EM, Totah J, Homan RW, Devous MD Sr, Bonte FJ. Interactive graphics method for regional quantification of tomographic brain blood flow images. *Proc Medcomp.* 1982:316-318.
25. Goldberg G. Supplementary motor area structure and function: review and hypotheses. *Behav Brain Sci.* 1985;8:567-616.
26. Hawver K. *A Comparison of the Performance of Stutterers and Nonstutterers on Tests of Central Auditory Processing.* Cincinnati, Ohio: University of Cincinnati; 1978. Doctoral dissertation.
27. Stager S, Freeman FJ, Finitzo-Hieber T. *Patterns of Auditory Brainstem Response in Stutterers.* Toronto, Ontario: American Speech Language Hearing Association; 1982.
28. Decker TN, Healy E, Howe S. Brainstem auditory characteristics of stutterers and nonstutterers: a preliminary report. *J Fluency Disord.* 1982;7:385-389.
29. Denays R, Tondeur M, Foulon M, et al. Regional brain blood flow in congenital dysphasia: studies with technetium-99m HM-PAO SPECT. *J Nucl Med.* 1989;30:1825-1829.
30. Billard C, Dulac O, Raynaud C, et al. Brain SPECT imaging in developmental childhood dysphasia. *J Nucl Med.* 1988;29:792.
31. Lou HC, Henriksen L, Bruhn P. Focal cerebral hypoperfusion in children with dysphasia and/or attention deficit disorder. *Arch Neurol.* 1984;41:825-829.

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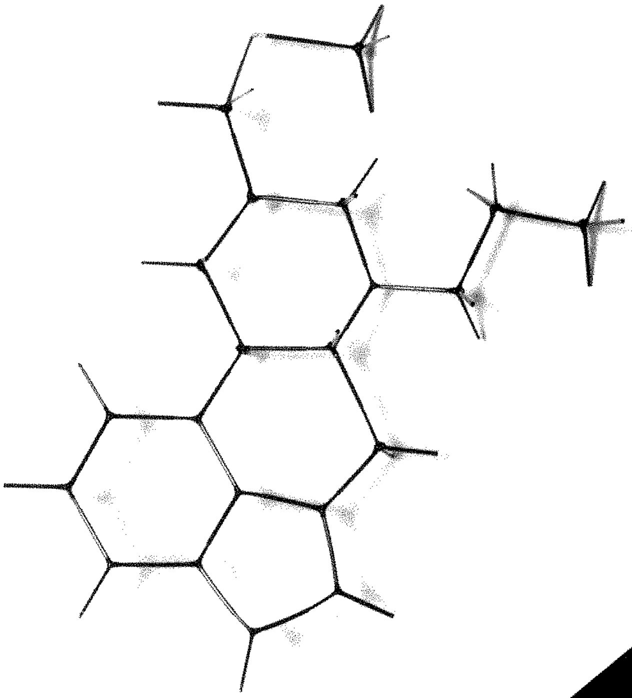

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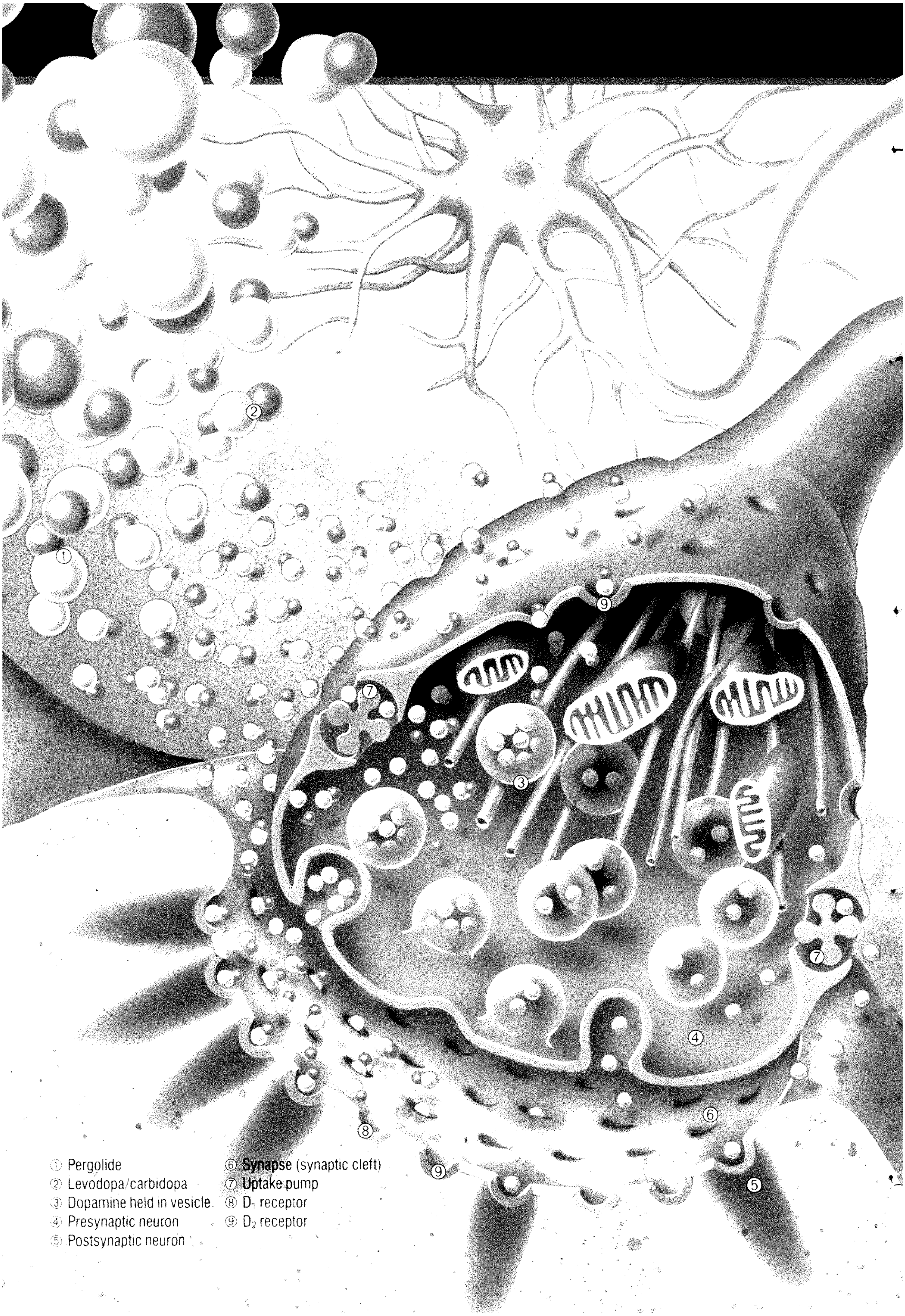

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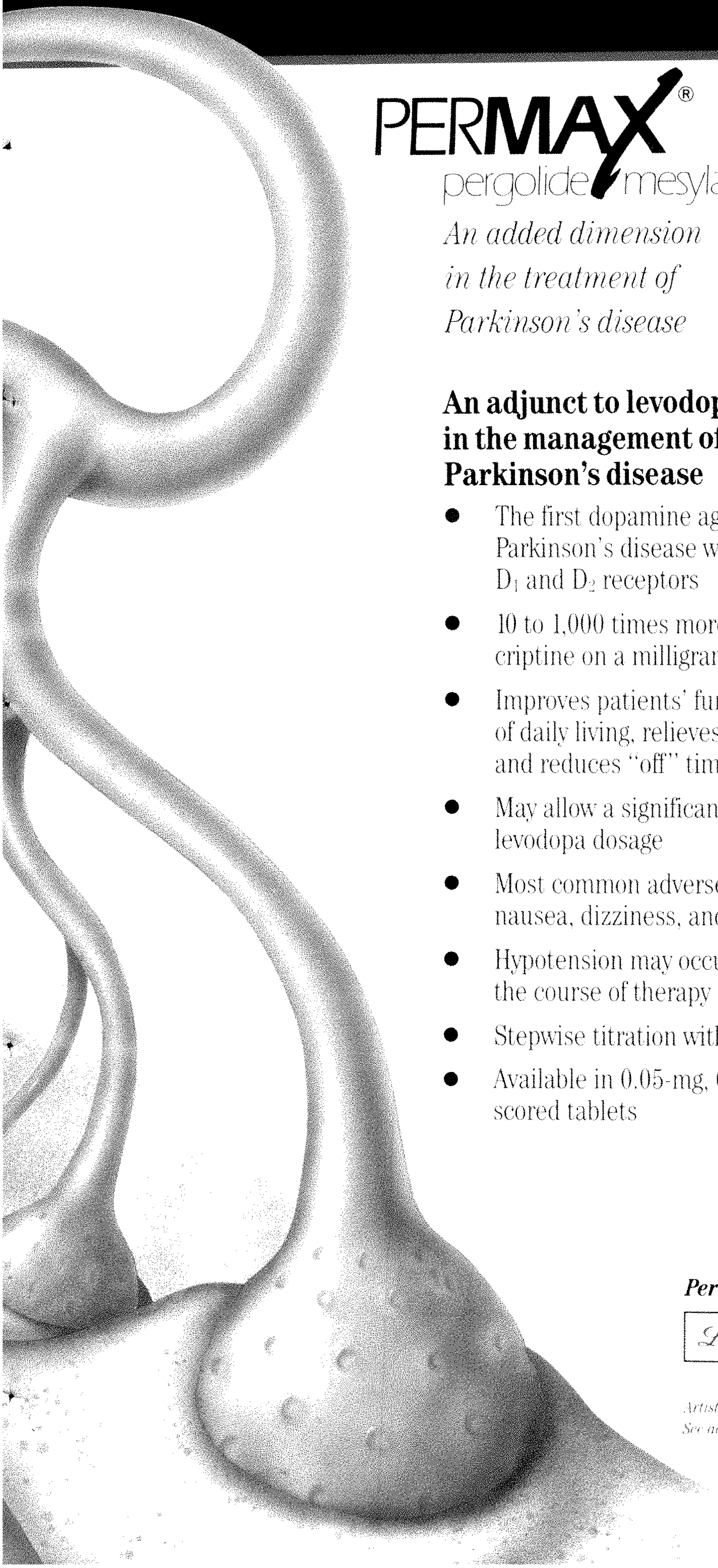

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Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

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There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities —*See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Events	
Body System/ Adverse Event*	Pergolide Mesylate N = 189	Placebo N = 187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.[illegible]
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax —This section reports event frequencies evaluated as of October 1988 for adverse event ocurring in a group of approximately 1,800 patients who took multiple dos pergolide mesylate. The conditions and duration of exposure to pergolid mesylate varied greatly, involving well-controlled studies as well as experienc in open and uncontrolled clinical settings. In the absence of appropriate cor trols in some of the studies, a causal relationship between these events an treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms c their relative frequency of reporting in the data base. Events of major clinica importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events ar defined as those occurring in at least 1/100 patients; infrequent adverse event are those occurring in 1/100 to 1/1,000 patients; rare events are those occu ring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, abdom inal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequen* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvi pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acut abdominal syndrome, LE syndrome.

Cardiovascular System —*Frequent:* postural hypotension, syncope, hype tension, palpitations, vasodilatations, congestive heart failure; *Infrequen* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogra angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystole cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atri fibrillation, varicose vein, pulmonary embolus, AV block, shoc *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart bloc cerebral hemorrhage.

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhea, co stipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver functio tests, increased appetite, salivary gland enlargement, thirst, gastroenteriti gastritis, periodontal abscess, intestinal obstruction, nausea and vomitin gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulce melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, pepti ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, coliti cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes melli tus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leukopenia lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblasti anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombo cythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System —*Frequent:* peripheral edema, weigh loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iro deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* elec trolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations, confu sion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams incoordination, psychosis, personality disorder, nervousness, choreoatheto sis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neu ropathy, neuralgia, hypertonia, delusion, convulsion, libido increased euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apa thy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brai edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voic alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequent:* ski discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpe zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, ski benign neoplasm, lichenoid dermatitis.

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media, con junctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract retinal detachment, retinal vascular disorder.

Urogenital System —*Frequent:* urinary tract infection, urinary frequency urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breas pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vagina hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

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Glutethimide Treatment of Disabling Action Tremor in Patients With Multiple Sclerosis and Traumatic Brain Injury

Mindy L. Aisen, MD; Mary Holzer, MS, OTR; Michael Rosen, PhD; Mark Dietz, MD; Fletcher McDowell, MD

• Glutethimide has been used to control essential tremor. Its efficacy in the treatment of disabling cerebellar and rubral tremor was assessed in an open study of six patients with multiple sclerosis and two patients with traumatic brain injury. Functional and quantitative tremor severity was assessed before treatment and 7 to 14 days after a stable dose was achieved. Six of eight patients exhibited visible functional benefit from treatment with glutethimide; abstract testing results correlated well with functional status in most cases. Four patients chose to continue to receive medication. Controlled trials of glutethimide to compare its efficacy with that of other medications used in the treatment of action tremor are indicated.

(*Arch Neurol.* 1991;48:513-515)

Glutethimide has been reported to suppress disabling essential tremor.[1] We studied the effects of glutethimide in eight patients with severe cerebellar tremor. Glutethimide is a piperidinedione derivative with sedative-hypnotic and anticholinergic effects. When first introduced, it was widely used as a general tranquilizer, for induction of anesthesia,[2] and as a hypnotic agent. Its popularity waned as concerns about its addictive potential surfaced.[3,4]

PATIENTS AND METHODS

Six patients with multiple sclerosis and two patients with traumatic brain injury were treated with gradually increasing doses of glutethimide (maximum stable doses, 750 to 1250 mg/d); all had disabling action tremor. The condition of seven patients did not respond to other drugs, including propranolol, clonazepam, amitriptyline, and isoniazid. Table 1 summarizes the clinical characteristics and prior therapies of six of the eight patients. Tremor was measured before treatment and 7 to 14 days after a stable dose was achieved. Two types of assessment were employed: functional and abstract.

Functional assessment was performed by a "blinded" occupational therapist. Subjects performed either a timed keyboard test coupled with a hoop test or a set of six function-like tasks derived from a standard clinical rating scale developed by Fahn and colleagues.[5] In the keyboard test, subjects were asked to tap five letter keys in a 1-minute period; the number accurately struck was the score. In the hoop test, subjects had to alternately encircle three 1.3-cm-diameter posts with a 15.2-cm-diameter hoop; the time elapsed to accurately perform the task was recorded. The clinical assessment scale included an estimated amplitude of tremor, handwriting, tracing an Archimedes spiral, pouring water from one cup to another, drinking/eating soup, and a keyboard test. The resulting score ranged from 0 to 32, with 0 reflecting no tremor.

The abstract method consisted of a pursuit-tracking task in which two images appeared on a computer screen. One image, the target, moved around the screen in a seemingly random pattern. The second image moved in response to motion at the end of a customized manipulator with the capacity to move in 3 *df*. The patient's limb was securely placed in a wrist-immobilizing splint affixed to the manipulator; movement in the limb therefore produced movement of the response image on the screen. The patient attempted to make the response image coincident with the target image. After an extended practice period, patients underwent tracking testing for 1-minute intervals. The practice period spanned several days, and data were sampled only after performance plateaued to minimize changes due to learning effects.

DATA ANALYSIS

An IBM-PC-AT–compatible computer (Leading Edge model D2, Leading Edge Corp, Westboro, Mass) with a monochrome screen was used for the tracking display. The display software, developed by Beringhause,[6] provided a seemingly random (repeat time, every 17 minutes) target that moved in the x and y directions at varying frequencies, with a range of 0.08 to 0.5 Hz. Target x and y screen coordinates were written to a hard disk file after each tracking experiment was completed. Data analysis methods developed by Adelstein et al[7,8] were used to derive quantitative measures of tracking fidelity and tremor magnitude. Both were believed to be important, because side effects of treatment (eg, sedation) might impair accuracy despite tremor suppression.

Tremor magnitude or tremor power was quantified by examination of the "residual" portion of the patient's response. The residual portion is that portion of the response signal not linearly related to the target signal. The residual autopower spectrum is calculated by multiplying the autopower spectrum of the response by 1 minus the coherence between the tracking and response signals. Tremor magnitude or tremor power was defined by the area under the residual response spectrum. Tracking fidelity, defined by the signal-to-noise ratio (SNR), was calculated by dividing the area under the target-response cross power density curve by the tremor power. Tremor power assessment provided information about changes in tremor amplitude, and SNR provided infor-

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Table 1.—Clinical Characteristics

Patient/ Sex/Age, y	Diagnosis*	Disease Duration, y	Prior Treatment
1/M/38	MS	5	Propranolol hydrochloride, clonazepam, amitriptyline hydrochloride
2/M/36	MS	8	None
3/F/41	MS	24	Isoniazid, propranolol, clonazepam
4/F/49	MS	20	Propranolol, clonazepam, amitriptyline
5/M/34	MS	12	Isoniazid, propranolol
6/M/29	TBI	8	Propranolol, amitriptyline
7/M/50	MS	15	Clonazepam, propranolol, amitriptyline
8/M/21	TBI	5	Clonazepam, propranolol, isoniazid

*MS indicates multiple sclerosis; TBI, traumatic brain injury.

Table 2.—Results of Functional Testing

	Hoop Test, No. of Seconds Required for 3 Correct Attempts		Keyboard, No. of Keys Correctly Struck in a 60-s Period	
Patient	Without Glutethimide	With Glutethimide	Without Glutethimide	With Glutethimide
1	...	...	2	4
2	...	...	3	3
3	34	23	2	4
4	33	26	2	3

	Six-Item Clinical Scale*	
	Without Glutethimide	With Glutethimide
5	26	18
6	16	10
7	19	13
8	20	22

*Possible score on the six-item clinical scale ranged from 0 to 32, with 0 reflecting no tremor.

Table 3.—Results of Abstract Testing

	Signal-to-Noise Ratio		Tremor Power	
Patient No.	Without Glutethimide	With Glutethimide	Without Glutethimide	With Glutethimide
1	166 (n = 3; SD = 51.6)	140 (n = 3; SD = 24.7)	11782 (n = 3; SD = 334.2)	12091 (n = 3; SD = 202.0)
2	20 (n = 3; SD = 8.1)	69 (n = 3; SD = 19.0)	15089 (n = 3; SD = 1612.0)	12242 (n = 3; SD = 2015.0)
3	70 (n = 2; SD = 10.0)	148 (n = 3; SD = 7.4)	46084 (n = 2; SD = 328.8)	1728 (n = 3; SD = 194)
4	16 (n = 5; SD = 3.0)	52 (n = 2; SD = 22.0)	18369 (n = 5; SD = 118.2)	14099 (n = 2; SD = 1483.5)
5	...	...	...	...
6	227 (n = 3; SD = 21.0)	331 (n = 2; SD = 17.7)	1533 (n = 3; SD = 232.5)	832 (n = 2; SD = 82.0)
7	105 (n = 4; SD = 15.5)	435 (n = 2; SD = 5.0)	4525 (n = 4; SD = 1832.6)	583 (n = 2; SD = 18.4)
8	140 (n = 3; SD = 23.6)	118 (n = 3; SD = 19.5)	2488 (n = 3; SD = 49.9)	2562 (n = 3; SD = 426)

mation about the quality of task performance. Therefore, if tremor suppression was associated with significant impairment due to fatigue or sedation, a decrease in tremor power would be accompanied by a stable or decreased SNR. A decrease in tremor power coupled with a rise in SNR reflected not only tremor reduction but also improved functional performance.

Tremor power and SNR values were generated for x and y dimensions. For the purpose of examining trends before and after glutethimide treatment, x and y values were combined to produce a single SNR and tremor power value for each trial.

RESULTS

Six patients demonstrated functional improvement after glutethimide treatment, one exhibited no change, and one worsened. Table 2 summarizes the results of functional testing.

As shown in Table 3, seven patients were tested by the abstract method: five improved and two worsened. In those who improved, SNR increased 110% to greater than 300%, and tremor power decreased 19% to 96%. An improvement in SNR was always concordant with improvement in tremor power within trials; the degree of improvement frequently varied considerably between these values. This may be due to combined tremor and ataxia in some subjects in whom tremor may be suppressed by medication, producing a decline in tremor power magnitude, but persistent incoordination prevents a proportional rise in SNR. Similarly, sedation may interfere with tracking fidelity even if tremor is suppressed.

Functional improvement correlated somewhat better with a patient's decision to continue therapy than did abstract improvement. Four patients chose to continue to receive treatment, as shown in Table 4. The primary side effect was sedation, and all patients who chose to discontinue glutethimide therapy experienced moderate to profound sedation while receiving the medication.

COMMENT

Six of eight patients exhibited visible functional benefits from treatment with glutethimide. In all but two patients, results of abstract testing correlated well with functional scores. Four of the six patients who exhibited functional improvement chose to continue treatment. All patients who discontinued medication exhibited persistent sedation, in contrast to prior experience with patients with essential tremor, in whom sedative effects rapidly resolved.[1]

Benefit did not relate to underlying diagnosis, as three of six patients with multiple sclerosis and one of two pa-

Table 4.—Testing Summary[*]

Patient	Glutethimide Dose, mg/d	Functional Testing	Abstract Testing	Side Effects	Continued Medication
1	750	I	W	Moderate sedation	Yes
2	750	N	I	Profound sedation	No
3	750	I	I	None	Yes
4	750	I	I	None	Yes
5	1000	I	Not performed	Moderate sedation, fatigue	No
6	1250	I	I	None	Yes
7	1000	I	I	Moderate sedation	No
8	750	W	W	Profound sedation	No

[*] I indicates improved; W, worsened; and N, no change.

tients with traumatic brain injury continued to receive medication, nor did it relate to clinical tremor characteristics. Both patients with traumatic brain injury exhibited rubral tremor, with prominent resting as well as kinetic components, while all patients with multiple sclerosis exhibited primarily action tremor. The patients with traumatic brain injury who responded demonstrated similar improvement in resting and kinetic tremor components.

The neural mechanism of the effect of glutethimide on tremor is unknown. Glutethimide is structurally similar to phenobarbital, sharing its sedative and anticonvulsant effects. It also stimulates substantial anticholinergic activity.[9] Sedative-hypnotic compounds, such as phenobarbital,[10] primidone,[11] and alcohol,[12] have documented abilities to attenuate essential tremor, and anticholinergic drugs are known to reduce resting tremor in Parkinson's disease. Little has been documented about the ability of either anticholinergic or sedative-hypnotic agents to ameliorate tremor due to dysfunction of the cerebellum or its connections. Controlled trials of glutethimide to compare its efficacy with that of other medications used in the treatment of disabling cerebellar and rubral tremor are indicated.

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References

1. McDowell FH. The use of glutethimide for treatment of essential tremor. *Mov Disord.* 1989;4:75-80.
2. Stephen CR, Duvoisin PM. Laboratory and clinical experience with glutethimide. *Anesthesiology.* 1960;21:482-488.
3. Cohen H. Primary glutethimide addiction. *N Y J Med.* 1960;60:280.
4. Sadwin A, Glen RS. Addiction to glutethimide (Doriden). *Am J Psychiatry.* 1958;115:469.
5. Fahn S, Tolosa E, Marin C. Clinical rating scale for tremor. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders.* Baltimore, Md: Urban & Schwarzenberg; 1988:255-234.
6. Beringhause S. *Viscously Damped Joystick for Proportional Control by Tremor Patients.* Cambridge, Mass: Department of Mechanical Engineering. Massachusetts Institute of Technology; 1988. Masters of Science Thesis.
7. Adelstein BD, Rosen M. Design of a two–degree-of freedom manipulandum for tremor research. In: *Proceedings of the Sixth Annual IEEE EMB Conference.* 1984:47-51.
8. Adelstein BD, Aisen ML, Rosen MJ. The effect of mechanical loads on essential tremor. *Neurology.* 1987;37(suppl):356. Abstract.
9. Turrian H, Gross F. Anticholinergische Eigenschaften hypnotisch und antikonvulsiv wirkender Gluthasaureimide. *Helv Physiol Pharmacol Acta.* 1958;16:208-221.
10. Baruzzi A, Procaccianti G, Martinelli P, et al. Phenobarbital and propranolol in essential tremor: a double-blind controlled clinical trial. *Neurology.* 1983;33:296-300.
11. Feely MP. Benign familial tremor treated with primidone. *BMJ.* 1981;282;740-741.
12. Growden JH, Shahani BT, Young RR. The effect of alcohol on essential tremor. *Neurology.* 1975;25:259-262.

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When patients describe the "hurt" of postherpetic neuralgia (PHN), they use a wide range of words to describe a pain that is often intractable and difficult to treat. Zostrix® (Capsaicin 0.025% w/w) Cream provides an effective topical treatment that alleviates intense pain in most PHN patients.

Topical Zostrix Works Where It Hurts

Zostrix®

(Capsaicin 0.025% w/w) Cream

Topical Analgesic

TARGETED ACTION
Acts on sensory nerves at site of application by selectively depleting substance P, a chemomediator of pain impulses along neuropathways.

EFFECTIVE
Alleviates the intense pain associated with postherpetic neuralgia in most patients. May also benefit patients when added to existing systemic drug regimens.

SAFE
No known interactions with systemic medications commonly prescribed for geriatric patients.

Topical Zostrix Works Where It Hurts

DESCRIPTION

Zostrix Cream contains capsaicin, 0.025% w/w, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

INDICATION

Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with rheumatoid arthritis and osteoarthritis.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken or irritated skin. Do not bandage tightly. If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

Adults and children 2 years of age and older: Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

HOW SUPPLIED

1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)

Store at room temperature.
U.S. Patent Nos. 4486450 and 5536404

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DRM-161D

Familial Inclusion Body Myositis Among Kurdish-Iranian Jews

Roberto Massa, MD; Boaz Weller, MD; George Karpati, MD; Eric Shoubridge, PhD; Stirling Carpenter, MD

• We report two cases of adult-onset, slowly progressive limb-girdle muscle weakness with a remarkable sparing of quadriceps muscles that developed in patients from different families of Iranian-Kurdish–Jewish origin. Each patient had a similarly affected sibling. The findings by means of muscle biopsies showed abnormalities typical of inclusion body myositis, including abundant lined vacuoles and characteristic cytoplasmic inclusions of 15- to 18-nm filaments. Remarkably, many vacuolated muscle fibers showed immunoreactivity to neural cell adhesion molecule, a fetal muscle antigen. The common origin of these patients from an isolated ethnic group with frequent consanguinity and the familial incidence is indicative of a genetic causation or predisposition, probably with an autosomal recessive inheritance. This familial myopathy is one of several clinical syndromes that share the typical pathological findings of inclusion body myositis. The pathogenic relationship between these different familial forms and the more common sporadic form of inclusion body myositis is not known.

(*Arch Neurol.* 1991;48:519-522)

Inclusion body myositis (IBM) is a distinct variety of idiopathic inflammatory myopathy. The usual features include slowly progressive muscle weakness starting in the sixth or seventh decade of life, male predominance, and resistance to corticosteroid therapy.[1,2] The diagnosis can only be confirmed by the finding of typical cytoplasmic and/or nuclear inclusions in muscle fibers, consisting of 15- to 18-nm filaments.[1] A resemblance of the filaments to paramyxovirus nucleocapsids and their reported immunoreactivity for mumps virus antigens implicated this virus in the causation of IBM,[3,4] but the results of recent studies have not supported this hypothesis.[5,6]

The pathological findings of IBM have also been reported as appearing in younger patients,[1,7-10] and several familial cases with atypical clinical features have been described.[10-14]

We have examined two patients from different families originating from an isolated Jewish population of Iranian Kurdistan, who presented with an adult-onset, slowly progressive myopathy. Each patient reported one similarly affected sibling. Light and electron microscopy of muscle biopsy specimens taken from both patients demonstrated the characteristic findings of IBM. In addition, an immunocytochemical study revealed an expression of neural cell adhesion molecule (nCAM) in most muscle fibers containing lined vacuoles.

REPORT OF CASES

CASE 1.— A 29-year-old woman, the second youngest of 10 children of a Jewish family from Iranian Kurdistan, developed, at the age of 20 years, proximal muscle weakness in the lower limbs, manifesting with difficulty climbing steps and getting up from a squatting position. Onset was gradual, and progression was slow but relentless. During her two pregnancies, there was considerable deterioration of muscle strength. Her examination showed extreme muscle atrophy and weakness of the lower extremity muscles, except the quadriceps that retained a near normal bulk and strength. The most severely affected muscles were the glutei, hip flexors, and hamstrings. In the upper extremities, muscle wasting and weakness were less prominent than in the lower limbs, and predominantly proximal. Neck flexors were moderately weak. There was no weakness of craniobulbar musculature. Tendon reflexes were absent except for weak knee jerks. Sensation was normal. The patient had an increased lumbar lordosis and a waddling gait. Her older brother, 45 years old, had a similar neuromuscular disease, but he was not available for evaluation.

CASE 2.— A 50-year-old woman, the second youngest of seven children of a Jewish family from Iranian Kurdistan, was apparently well until the age of 40 years, when she first noticed instability of gait due to weakness in both lower extremities. Over the years, the leg weakness gradually progressed, and she developed difficulty walking upstairs. About 4 years prior to examination, she noticed weakness of both upper extremities, more marked distally. Examination showed marked atrophy of intrinsic hand muscles. There was asymmetrical weakness in the upper extremities, more marked on the left; it was of moderate degree in the shoulder girdle, slightly more marked in the biceps and triceps, and severe in the forearm and small hand muscles. There was no obvious wasting of lower extremity muscles. There was marked weakness of hip flexors, glutei, hamstrings, and foot dorsiflexors. The strength in the quadriceps and plantar flexors was remarkably preserved. The neck flexors were moderately weak. There was no weakness of craniobulbar musculature. Tendon reflexes were present throughout, but barely elicitable at the ankles. Sensation was normal. She had a markedly waddling and steppage gait. Her only sister, 65 years old, was reported to have a similar neuromuscular disease, but she was not available for examination. The three children (one male and two female) of the proband were examined by us; none of them showed neurological abnormality.

MATERIALS AND METHODS

A biopsy of the biceps brachii muscle was performed in both patients and the biopsy specimens were processed for histochemical, phase, and electron microscopic examination, as previously described.[15] In addition, the expression of immunoreactive class I major histocompatibility complex (MHC I) and nCAM was determined on 4-µm-thick, transverse cryostat sections, by means of the immunoperoxidase technique.[16] An antihuman MHC I monoclonal antibody (PHM4, Cedarlane Laboratories, Hornby, Ontario), at a dilution of 1:50, and an antihuman nCAM monoclonal antibody, undiluted (5.1H11), were used as primary antibodies. Hybri-

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doma cells secreting the 5.1H11 antibody (cloned by Dr F. Walsh, Institute of Neurology, Queens Square, London, United Kingdom) were grown in Dulbecco's modified Eagle medium plus hypoxanthine-aminopterin-thymidine medium plus 10% fetal calf serum. The supernatant from pelleted cells was used as the source of the antibody.

RESULTS

Laboratory Examination

Results of laboratory investigations are presented in the Table. Additionally performed immunological tests, including quantitative immunoglobulin levels and erythrocyte sedimentation rate, revealed normal results in both patients.

Muscle Biopsy

Both biopsy specimens demonstrated the characteristic findings of IBM on histochemical, phase, and electron microscopic examination.[1] Histochemical study of cryostat sections revealed many small-caliber muscle fibers, some of which were extremely atrophic (Fig 1). In case 1, there was a tendency for small-caliber fibers to occur in groups. Other fibers were clearly hypertrophic, with a rounded cross-sectional outline. There was a substantial increase in endomysial connective tissue (Fig 1), and in some regions large adipocytes were present between muscle fibers. This was particularly conspicuous in case 2. Centrally situated myonuclei were increased in number. The myonuclei appeared abnormal in many instances: some were enlarged and pale, while others were enlarged and hyperchromatic. Some nuclei contained inclusions (Fig 2, left); some pyknotic nuclear clumps were also present. About one third (case 1) to half (case 2) of the muscle fibers contained vacuolar spaces (Fig 1). Many fibers had multiple spaces, whose size varied from a few micrometers to as much as 30 μm in largest dimension. Some vacuoles were optically empty, but in others there was ill-defined debris along with punctate basophilic granules (Fig 1). Nuclei frequently were present within the vacuolar spaces. Some vacuoles contained impressive eosinophilic inclusions (Fig 2, left and right). There were a few examples of necrosis and phagocytosis of muscle fibers (Fig 3), as well as regener-

Summary of Laboratory Investigations

Test	Patient 1	Patient 2
Serum creatine kinase,* IU/dL	404	159
Electromyography	Polyphasic motor unit potentials, fibrillations	Small, polyphasic motor unit potentials, fibrillations, positive sharp waves
Nerve conduction velocity	Normal	Normal
Brain magnetic resonance imaging	Normal	Not performed
Brain magnetic resonance spectroscopy	Not performed	Normal

*Normal range, 5-140 IU/dL.

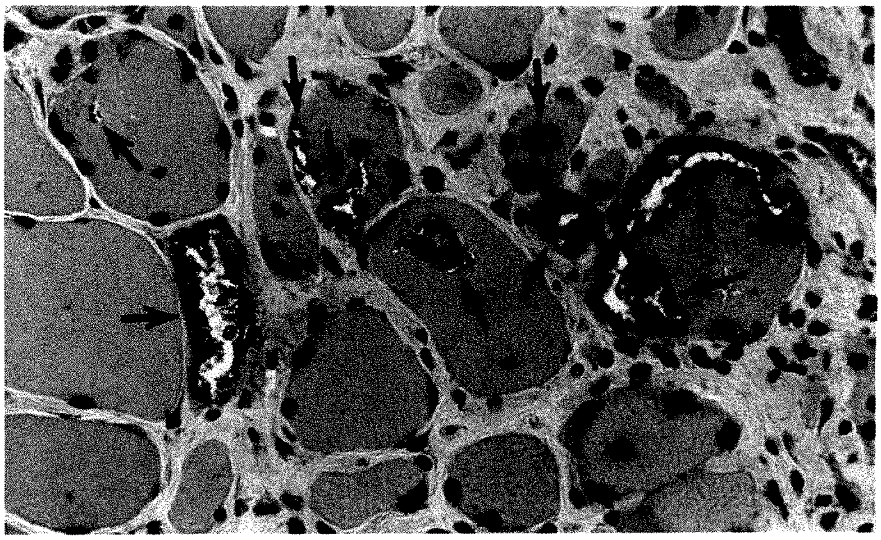
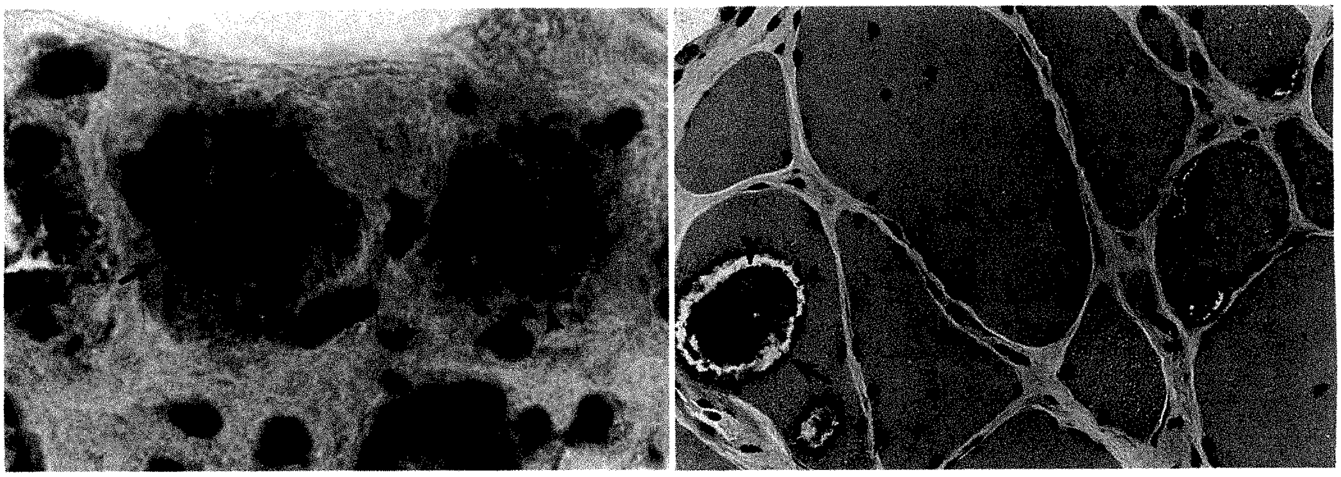


Fig 1.—Patient 2. Several normal-sized or atrophic fibers contain conspicuous small or large lined vacuoles (arrows). There are scattered rounded atrophic fibers, some of which contain central myonuclei. The endomysial connective tissue is markedly increased (hematoxylin-eosin, original magnification ×350).

Fig 2.—Left, Patient 2. Large nuclear (arrow) and cytoplasmic (arrowhead) inclusions are present in two very small muscle fibers. The nuclear inclusion causes a marked peripheral crowding of the chromatin. Right, Patient 1. Two conspicuous inclusions (arrowheads) are intermingled with the contents of a large lined vacuole (arrow) (hematoxylin-eosin, original magnification left, ×1400; right, ×350).



ation. A few small mononuclear inflammatory infiltrates were seen between muscle fibers (Fig 3). Both the necrotic fibers undergoing phagocytosis and some scattered regenerating fibers showed moderate to strong expression of MHC I. A few of the fibers containing lined vacuoles were also moderately positive. On the other hand, most of the fibers containing lined vacuoles, although not all of them, showed moderate to strong immunoreactivity for nCAM, either localized to the sarcolemma or, most commonly, evenly distributed throughout the cross-sectional area of the fiber (Fig 4). Regenerating fibers were also nCAM positive. There was no immunoreactive nCAM in vacuole-bearing muscle fibers found in biopsy specimens of four patients with typical, sporadic IBM.

Phase microscopy on resin sections showed that many fibers contained dark granules. In some large fibers, there were foci of Z-disk streaming. Electron microscopy showed membranous whorls and accumulations of characteristic filaments (15 to 18 nm in diameter) in the cytoplasm of several myofibers (Fig 5). Filaments were not found in nuclei in the sections examined.

COMMENT

Our patients presented with a progressive myopathy with onset in the third and fourth decade of life, respectively. The pathological features in both cases were indistinguishable from those of sporadic IBM. Variations in fiber caliber, lined (rimmed) vacuoles, necrotic and regenerating fibers, proliferation of endomysial connective tissue, membranous whorls, and inclusions composed of 15- to 18-nm filaments were found. All these features are characteristic and, in combination, have been considered pathognomonic of IBM.[1,2] The degree of the pathological changes in our patients, especially in patient 2, seemed to be more severe than that in the common sporadic cases of IBM. The pattern of MHC I expression was consistent with that previously described for sporadic IBM.[16] Interestingly, the expression of nCAM was detected by the 5.1H11 antibody in most of the myofibers containing lined vacuoles. Reactivity to this antibody, which is now known to recognize human nCAM,[17] was originally thought to be restricted to human myoblasts, myotubes, and regenerating fibers in diseased adult muscle.[18] However, we have detected a similar reactivity in vacuolated fibers in cases of sporadic IBM, oculopharyngeal muscular dystrophy, and colchicine myopathy, in addition to denervated fibers (manuscript in preparation). In all these instances,

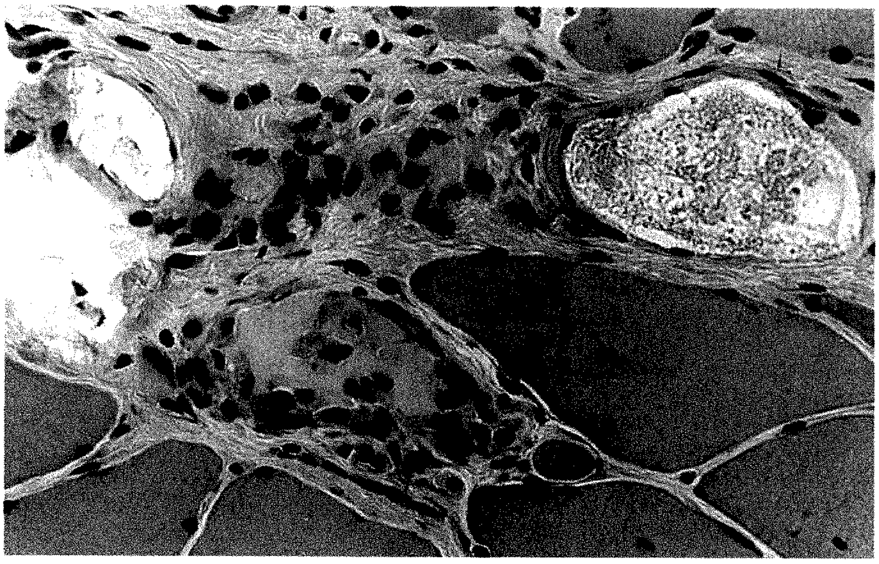


Fig 3.—Patient 1. Mononuclear inflammatory cells are present in the vicinity of a large vein with a necrotic fiber (lower part of the picture) undergoing phagocytosis (hematoxylin-eosin, original magnification ×350).

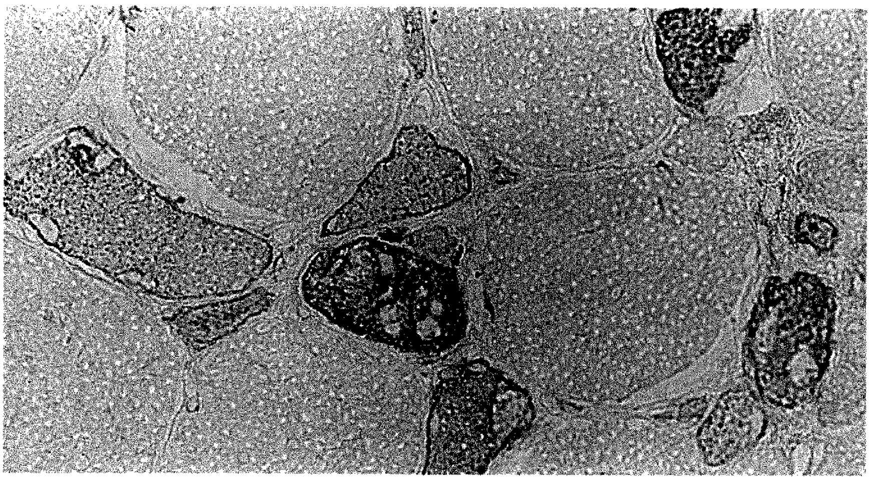
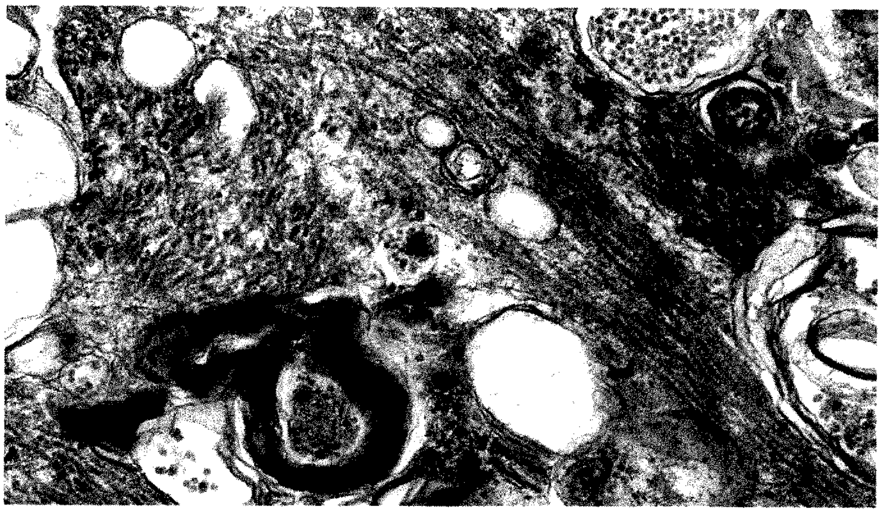


Fig 4.—Patient 1. Several fibers show both diffuse and punctate cytoplasmic, as well as sarcolemmal, immunoreactive neural cell adhesion molecule. The majority of the positive fibers harbor conspicuous lined vacuoles (immunoperoxidase using anti–neural cell adhesion molecule antibody [5.1H11] and biotin-streptavidin display systems, original magnification ×350).

Fig 5.—Patient 2. Electron micrograph shows abnormal 15- to 18-nm filaments characteristic of inclusion body myositis surrounded by small membranous whorls (original magnification ×40 000).



myofibers might undergo a process of dedifferentiation, leading to reexpression of fetal antigens such as nCAM.

The clinical picture observed in these patients is also consistent with the usual presentation of IBM, with two exceptions: one is the relatively early onset, and the other is a striking sparing of quadriceps muscles. Inclusion body myositis most often begins in the sixth or seventh decade of life, although some cases have been described beginning as early as the second decade.[7-10] The remarkable sparing of quadriceps muscles, even when all other muscles in the lower extremities show practically complete paralysis (as was the case in patient 1), makes this syndrome phenotypically distinct.

Both our patients reported one sibling having similar symptoms. These persons were not available for clinical examination, but the description of their symptoms is consistent with progressive weakness of proximal limb muscles. This suggests a familial incidence of IBM in these cases.

Although there is no direct evidence of consanguinity within or between these two families, they have a common origin in a small and isolated Jewish population in Iranian Kurdistan, with a high frequency of intermarriages. The familial incidence and the geographic segregation are indicative of a genetic causation or predisposition, probably inherited as an autosomal recessive trait. The reported absence of weakness in the parents of the patients and the absence of clinical findings in the children of patient 2 are consistent with this suggestion. However, a future onset of the disease in the latest generation cannot be completely ruled out at this point.

A number of articles have described the presence of rimmed vacuoles and the typical cytoplasmic or nuclear filaments in patients with undefined familial myopathies. Matsubara and Tanabe[11] reported these pathological findings in two siblings with an autosomal recessive, progressive distal myopathy developing during the third decade of life. Eisen et al[10] described a progressive distal myopathy with onset in early childhood in a man whose muscle biopsy specimen revealed the typical findings of IBM. His brother was affected with a similar illness, but he was not studied. Fukuhara et al[12] reported a "variant form of oculopharyngeal muscular dystrophy" in a man with onset in the third decade of life. His son developed a distal myopathy during infancy. Examination of muscle biopsy specimens taken from these patients showed rimmed vacuoles. Electron microscopic findings in the son demonstrated cytoplasmic inclusions consisting of 13- to 19-nm filaments. Cole et al[13] investigated a family in which five of six male siblings were affected by a progressive myopathy beginning in early childhood. Examination of muscle biopsy specimens obtained from all patients revealed the characteristic findings of IBM. Four of these patients presented an additional feature, ie, a markedly abnormal appearance of cerebral white matter on computed tomographic scan and magnetic resonance imaging of the brain. There was no clinical or other laboratory evidence of a white matter dysfunction. Sunohara et al[14] described five Japanese patients from three families, presenting a progressive distal myopathy with onset in early adulthood. Pathological findings included rimmed vacuoles and, in some cases, typical intranuclear filaments. The disease was probably inherited as an autosomal recessive trait.

The patients whom we describe here share the same pathological findings with the other reported examples of familial IBM. On the other hand, their clinical presentation included neither oculopharyngeal involvement nor a predominantly distal weakness. In addition, there was no evidence of white matter abnormality by means of magnetic resonance imaging or spectroscopy, respectively, in our two patients. For these reasons, we suggest that our patients represent a distinct form of familial IBM peculiar to their ethnic group.

Although no previous familial cases of IBM in Iranian Kurdish Jews have, to our knowledge, been reported, we found that a "rimmed vacuole myopathy" in Iranian Jews was described by Argov and Yarom.[19] They investigated the condition of nine patients from four families, with a progressive generalized myopathy sparing the quadriceps that had begun in the third or fourth decade of their life. These authors also emphasized the conspicuous sparing of quadriceps muscles. Muscle biopsy specimens were characterized by the presence of rimmed vacuoles. Abnormal filaments were not mentioned in the description of the two cases processed for electron microscopic examination. Inheritance was believed to be autosomal recessive. Our cases share many features with the above-mentioned ones, such as Iranian-Jewish origin; probable autosomal recessive inheritance; age at onset of disease; distribution of weakness, including the notable preservation of quadriceps; and the light microscopic findings. We believe, therefore, that our patients and those described by Argov and Yarom[19] represent the same entity.

This familial myopathy is a further indication that several clinical syndromes share the typical pathological findings of IBM. The understanding of the pathogenetic mechanism(s) at the molecular level will clarify the relationship between the sporadic form and the present and other familial forms of IBM.

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We thank Peter Ashby, MD, who referred case 1 and Donald W. Baxter, MD, who referred case 2.

References

1. Carpenter S, Karpati G, Heller I, Eisen A. Inclusion body myositis: a distinct variety of idiopathic inflammatory myopathy. *Neurology.* 1978; 28:8-17.
2. Lotz BP, Engel AG, Nishino H, et al. Inclusion body myositis: observations in 40 patients. *Brain.* 1989;112:727-747.
3. Chou SM. Myxovirus-like structures in a case of human chronic polymyositis. *Science.* 1967; 158:1453-1455.
4. Chou SM. Inclusion body myositis: a chronic persistent mumps myositis? *Hum Pathol* 1986; 17:765-777.
5. Rammohan KW, Wolinsky J, Omerza J, et al. Mumps virus in IBM: studies implicating cross-reactivity accounting for antigen localization. *Neurology.* 1988;38(suppl 1):151.
6. Nishino H, Engel AG, Rima BK. Inclusion body myositis: the mumps virus hypothesis. *Ann Neurol.* 1989;25:260-264.
7. Sato T, Walker DL, Peters HA, et al. Myxovirus-like inclusion bodies in chronic polymyositis: electron microscopic and viral studies. *Trans Am Neurol Assoc.* 1969;94:339-341.
8. Yunis EJ, Samaha FJ. Inclusion body myositis. *Lab Invest.* 1971;25:240-248.
9. Tomé FMS, Fardeau M, Lebon P, Chevallay M. Inclusion body myositis. *Acta Neuropathol.* 1981;(suppl 7):287-291.
10. Eisen A, Berry K, Gibson G. Inclusion body myositis (IBM): myopathy or neuropathy? *Neurology.* 1983;33:1109-1114.
11. Matsubara S, Tanabe H. Hereditary distal myopathy with filamentous inclusions. *Acta Neurol Scand.* 1982;65:363-368.
12. Fukuhara N, Kumamoto T, Tsubaki T, et al. Oculopharyngeal muscular dystrophy and distal myopathy. *Acta Neurol Scand.* 1982;65:458-467.
13. Cole AJ, Kuzniecky R, Karpati G, et al. Familial myopathy with changes resembling inclusion body myositis and periventricular leucoencephalopathy. *Brain.* 1988;111:1025-1037.
14. Sunohara N, Nonaka I, Kamei N, Satoyoshi E. Distal myopathy with rimmed vacuole formation. *Brain.* 1989;112:65-83.
15. Carpenter S, Karpati G. Methods of tissue removal and preparation. In: *Pathology of Skeletal Muscle.* New York, NY: Churchill Livingstone Inc; 1984:39-61.
16. Karpati G, Pouliot Y, Carpenter S. Expression of immunoreactive major histocompatibility complex products in human skeletal muscles. *Ann Neurol.* 1988;23:64-72.
17. Walsh FS, Dickson G, Moore SE, Barton CH. Unmasking N-CAM. *Nature.* 1989;339:516.
18. Hurko D, Walsh FS. Human fetal muscle-specific antigen is restricted to regenerating myofibers in diseased adult muscle. *Neurology.* 1983;33:737-743.
19. Argov Z, Yarom R. 'Rimmed vacuole myopathy' sparing the quadriceps. *J Neurol Sci.* 1984;64:33-43.

Altered Cutaneous Sensation in Trigeminal Neuralgia

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• Noninvasive quantitative somatosensory tests were used to measure sensory perception thresholds on the faces of 26 patients with idiopathic trigeminal neuralgia. The affected divisions were determined by the presence of trigger zones. Elevations of thresholds of sensations subserved by both large- and small-diameter fibers were found both in the affected and in the unaffected adjacent divisions when compared with the healthy side. The findings are interpreted as further evidence of combined peripheral and central pathologic conditions in idiopathic trigeminal neuralgia.

(*Arch Neurol.* 1991;48:523-527)

The diagnosis of tic douloureux, or idiopathic trigeminal neuralgia (ITN), is based on the history of mechanically elicited pain paroxysms and the absence of neurological deficits on routine examination.[1-3] Any sensory abnormality observed by the clinician is considered to prompt careful neuroradiological and laboratory evaluation to exclude treatable causes for the condition, such as local tumors, vascular malformations, infections, and multiple sclerosis plaques.[2,4,5] Yet many authors refer to occasional sensory findings in patients with ITN, although no systematic data are presented.[4,6-9] There is also some evidence of electrophysiological abnormalities in this condition,[10,11] although conflicting results have also been reported, even from the same laboratory.[12-14] Histopathological changes as well as completely normal results have been described at various levels of the trigeminal pathway,[15-17] and since it is not clear whether the findings represent genuine or postmortem changes, caution in interpretation is recommended.[2]

While the etiopathogenesis of ITN remains largely unresolved, evidence has been accumulating from animal and human studies making it difficult to explain the characteristics of this capricious pain condition without considering both central and peripheral factors.[9,18-20] Pain paroxysms set off by innocuous stimuli within the trigger zones and outlasting the duration of the stimulus,[9,18] radiation of pain outside the involved territory,[18] and efficacy of drugs capable of facilitating segmental or afferent inhibition in the trigeminal nuclei[19] are best explained by central pathophysiology. On the other hand, observations of compression, distortion, or stretching of the trigeminal nerve[7,21] as well as relief provided by various procedures affecting the nerve practically anywhere along its course[3,22,23] stress the significance of the peripheral input. Why does facial sensation in ITN escape the slightest impairment despite an obvious trigeminal pathway dysfunction, as generally assumed?

The aim of the present study was to ascertain whether, in fact, sensory abnormalities can be found in ITN by using systematic and quantitated somatosensory measurements and, if so, whether they elucidate the pathogenetic mechanisms in this condition. Sensory thresholds in the affected divisions and outside the affected divisions on the painful side of the face were measured and compared with those of the contralateral homologous sites in a group of patients suffering from ITN. Because of the well-known problem of correctly assessing the exact situation and distribution of the pain,[2] an approach of searching for cutaneous and mucosal trigger zones and naming the affected division accordingly was chosen. The results presented here are suggestive of changes in the trigeminal somatosensory system, found not only in the affected but in the adjacent nonsymptomatic divisions as well.

PATIENTS AND METHODS

Patients

Twenty-six patients with a history of ITN (tic douloureux) and one or several clinically verifiable trigger zones within the trigeminal nerve distribution participated in the study. The ITN was diagnosed after the patient presented a history of pain with the following characteristics: (1) electric, shock-like, stabbing pains; (2) pain of abrupt onset and abrupt termination; (3) painfree intervals between attacks; (4) unilateral pain during an attack and restricted to a zone innervated by the trigeminal nerve; and (5) attacks triggered by local nonnoxious stimulation.[3,20] In 17 patients, pain occurred on the right side and in nine patients on the left side. The mean age was 65.8 years (range, 47 to 81 years); female-to-male ratio, 22:4; and mean duration of ITN, 58.6 months (range, 2 to 180 months). No patient had undergone neurosurgical operations or received nerve blocks. All but two patients were receiving a carbamazepine during the tests with dosage ranging from 200 to 1200 mg daily; three patients used baclofen in addition. Accord-

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ing to recent recommendations,[20] no routine radiological investigations were carried out, but any suspicion of a neurological disease raised by the sensory findings of the ongoing study prompted a computed tomographic evaluation with special attention to the basal structures of the brain. A computed tomographic scan of the brain was judged necessary in 15 patients and turned out normal in each case. Nineteen patients eventually had surgery (radiofrequency or glycerol gangliolysis, 17 patients; microvascular decompression, two patients). The final diagnosis of ITN was agreed on by at least two specialists (a neurologist and a neurosurgeon).

Excluded from the study were those patients with a history of head trauma, mental disease, alcohol or drug abuse, severe systemic or metabolic disease, and any major neurological disease. None of the patients had a history suggestive of incipient dementia. All patients gave informed consent.

Trigger zones were systematically assessed and localized as accurately as possible. This was done by gently tapping the skin of the face or the intraoral mucosa with a small glass rod. Because almost all patients were taking medication, actual tics developing into fullblown trigeminal attacks were not anticipated. To qualify for a trigger zone, a spot on the skin or mucosa had to be recognized, by the patient, as frankly painful on touching and a shooting sensation away from it had to be present. In this fashion, definite trigger zones were elicited in 28 divisions in 26 patients. They were found only in the second and third division. Some patients gave a history of pain paroxysms extending outside the trigger zones as reported before.[18,24] Some patients reported migration of trigger zones over the years.[9] Summary of clinical data is presented in Table 1.

Table 1.—Clinical Characteristics of the Patients*

Patient No./ Age, y/Sex	Duration of ITN, mo	Distribution of Pain	Trigger Zones	Medical Therapy of ITN	
				Medication	Daily Dose, mg
1/67/F	24	V2, V3	V2	C	800
2/64/F	51	V2, V3	V3	C	400
3/65/M	60	V3	V3	C	1000
4/63/F	56	V2	V2	Nil	...
5/73/F	144	V1, V2	V2	C	300
6/75/F	2	V2	V2	Nil	...
7/79/F	18	V2	V2	C	800
8/56/F	60	V2, V3	V2	C	300
9/69/F	108	V3	V3	C	200
10/56/F	10	V2	V2	C	200
11/47/F	72	V2, V3	V2	C	400
12/66/M	48	V2, V3	V2, V3	C	800
13/70/F	72	V2	V2	C	300
14/68/F	94	V2	V2	C	800
15/58/F	24	V3	V3	C	1200
16/72/F	14	V2, V3	V2, V3	C	1200
17/81/F	70	V2	V2	C	1000
18/63/F	52	V2	V2	C and B	400 and 15
19/75/F	6	V3	V3	C and B	800 and 25
20/73/F	91	V3	V3	C	1000
21/52/F	24	V2	V2	C	600
22/55/F	18	V1, V2	V2	C	400
23/58/M	120	V2, V3	V2	C and B	800 and 30
24/55/F	34	V2	V2	C	600
25/80/M	180	V2	V2	C	600
26/71/F	72	V2	V2	C	400

*ITN indicates idiopathic trigeminal neuralgia; V1, ophthalmic division; V2, maxillary division; V3, mandibular division; C, carbamazepine; B, baclofen; Nil, no medication.

Methods

Measurements were carried out in quiet laboratory conditions, after a careful explanation of used methods. All six trigeminal divisions (ophthalmic [V1], maxillary [V2], and mandibular [V3], bilaterally) were tested in randomized order. In order not to accidentally cross the boundaries between two adjoining dermatomes, the measuring sites were restricted to those shown by the shaded areas in the Figure. If a pain paroxysm was inadvertently evoked by trigger zone exploration, then a period of 30 minutes was allowed to pass before resuming the test.

Warm, cold, hot pain, and cold pain thresholds were measured with the Thermotest (Somedic AB, Stockholm, Sweden) using a modification of the Marstock technique.[25,26] A Peltier-type thermode 3.6 cm^2 in size was warmed up or cooled down at a rate of 0.5°C to 1.5°C per second. Measurements started from an adapting temperature of 30°C. The patients responded to each individual thermal sensation by pressing a switch that reversed the direction of temperature change and allowed the thermode to return to the baseline temperature. Each measurement was done three to five times, and the average was calculated. Cold pain was measured once; a cutoff point was determined at 5°C. The results were expressed in degrees centigrade.

Tactile sensation was measured with von Frey filaments of equal length and varying diameters (Pressure Aesthesiometer, Stoelting Co, Chicago, Ill), which were applied in descending and ascending order of magnitude to assess both the disappearance and appearance thresholds (at least five applications per filament). Care was taken to avoid stroking the skin with the hair and to only do an indentation. The force required to bend each filament (in grams) was converted to log units.

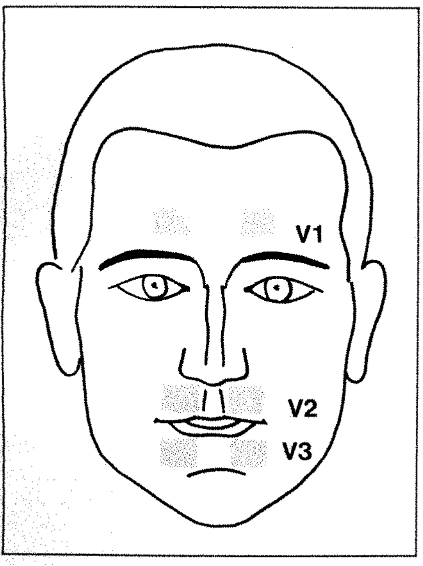
Pinprick sensation was tested with weighted needles.[26] The needles (25-mm, 24-gauge needles weighing from 0.2 to 5.2 g) were on the plungers of 5-mL plastic syringes moving freely. By holding the syringe, the examiner could guide the needle of any weight perpendicularly to the area tested; in essence, it was only the weight of the needle that determined the force and subsequent pinprick sensation. The patient reclined and was verbally cued before each stimulus to ensure attention. Similarly to tactile stimulation, this test was carried out in a descending and ascending manner, each application repeated at least five times. The results were expressed in milligrams.

Two-point discrimination was measured with a Weber's compass, moving the instrument gently on the tested skin area to improve sensitivity.[27] Three ascending and descending series in increments of 1 to 2 mm were administered in alternating order. The results were expressed in millimeters.

Temperature was measured in each division, after acclimatization in a draft-free room for 20 minutes, by means of free thermocouples attached to the skin (Digitron Instruments, model 4071, Hertford, United Kingdom) and expressed in degrees centigrade.

For each somatosensory threshold, comparisons were made between the painful side and the contralateral side. Results from measurements were pooled to form two pairs representing different measurement sites as follows: (1*a*) affected divisions characterized by the presence of trigger zones (TRI-IPS), (1*b*) contralateral mirror-image divisions (TRI-MIR), (2*a*) unaffected, trigger-free divisions ipsilateral to 1*a* (ADJ-IPS), and (2*b*) contralateral mirror-image divisions (ADJ-MIR). By the definition adopted for this study, in a patient with a trigger zone confined to the V3 division, the adjacent division automatically was the maxillary (V2) division. In a patient with trigger zones confined to the V2 division, both ophthalmic (V1) and mandibular (V3) divisions were designated as adjacent. In a patient with trigger zones found in both V2 and V3 divisions, the adjacent division, of course, was the ophthalmic division. In this fashion, 28 affected divisions and 44 adjacent divisions were arrived at.

In both sets of comparison, significances between differences of means of perception thresholds in the corresponding divisions



Sites chosen for measuring the somatosensory perception thresholds. The trigeminal divisions are as follows: V1, ophthalmic; V2, maxillary; and V3, mandibular.

Table 2.—Somatosensory Perception Thresholds in Patients With Idiopathic Trigeminal Neuralgia: Affected Divisions*

	Divisions		
Threshold	**TRI-IPS**	**TRI-MIR**	P†
Warm, °C	33.9 (0.3)	33.1 (0.2)	<.0005
Cold, °C	28.7 (0.2)	28.7 (0.2)	NS
Hot pain, °C	42.4 (0.7)	42.2 (0.7)	NS
Cold pain, °C	9.9 (1.3)	9.0 (1.1)	NS
Pinprick, mg	584 (120)	410 (52)	NS
Touch, log$_{10}$0.1 mg	2.43 (0.11)	2.13 (0.09)	<.002
2-point discrimination, mm	10.5 (0.9)	10.4 (0.8)	NS

*TRI-IPS indicates affected division with trigger zones; TRI-MIR, contralateral mirror-image division; and NS, not significant. All values are the mean (SEM).

†P values given in levels of significance for differences between the symptomatic and the contralateral side (Student's *t* test for paired samples, two tailed). To compensate for multiple comparisons, the significance level was set at $P < .007$.[28]

Table 3.—Somatosensory Perception Thresholds in Patients With Idiopathic Trigeminal Neuralgia: Adjacent Divisions*

	Divisions		
Threshold	**ADJ-IPS**	**ADJ-MIR**	P†
Warm, °C	33.9 (0.3)	33.3 (0.2)	<.005
Cold, °C	28.6 (0.2)	28.7 (0.2)	NS
Hot pain, °C	43.7 (0.5)	43.2 (0.5)	<.005
Cold pain, °C	9.3 (1.0)	9.8 (0.9)	NS
Pinprick, mg	562 (85)	446 (82)	NS
Touch, log$_{10}$ 0.1 mg	2.35 (0.07)	2.23 (0.07)	.015 (NS)
2-point discrimination, mm	10.9 (0.7)	9.6 (0.6)	<.0005

*ADJ-IPS indicates adjacent trigger zone free division, ipsilateral to TRI-IPS; ADJ-MIR, mirror-image division; and NS, not significant. All values are the mean (SEM).

†P values given in levels of significance for differences between the symptomatic and the contralateral side (Student's *t* test for paired samples, two tailed). To compensate for multiple comparisons, the significance level was set at $P < .007$.[28]

were analyzed using Student's two-tailed *t* test for paired samples. Due to multiple comparisons, a Bonferroni correction procedure to adjust the significance level was employed. The correction was obtained by dividing the alpha level by the total number of comparisons in each set. For seven pairwise a priori comparisons, the significance level was scaled down to $P < .05/7 = 0.007$.[28]

RESULTS

In the affected divisions (TRI-IPS), elevated warm and tactile thresholds were observed when compared with those in the mirror-image divisions (TRI-MIR). In the adjacent (ADJ-IPS) divisions, comparison with the contralateral divisions (ADJ-MIR) revealed significant elevations of warm, hot pain, and two-point discrimination thresholds, while a change of tactile threshold demonstrated an apparent trend for significance. The results are summarized in Tables 2 and 3.

Because medication may have an effect on perception, direct comparisons of the individual somatosensory thresholds with the available normative data were considered inappropriate. It seemed reasonable, however, to assume that medication would not significantly interfere with the degree of sensory asymmetry between the two sides of the face. From a group of healthy subjects of comparable age and sex distribution (n = 20; mean age [SD], 68.5 [9.2] years; female-to-male ratio, 12:8) who underwent the same tests in all six trigeminal divisions, mean asymmetry indexes (defined as the ratio between right and left sides) and standard deviations were calculated for each level. Any sensory function measured in the patient with ITN was defined as abnormal if the degree of asymmetry, ie, measured values between the affected and the contralateral side, exceeded the control group mean by at least 3 SDs. Abnormalities of thermal thresholds were found in eight patients, tactile thresholds in eight, pinprick thresholds in four, and two-point discrimination in three patients. When the results were combined, 15 of 26 patients showed at least one abnormal measure of sensation, mainly a threshold elevation in TRI-IPS or ADJ-IPS divisions, or both. In only one patient was there an abnormally low threshold (for hot pain in the TRI-IPS division).

There were no temperature asymmetries (TRI-IPS of 31.0 ± 0.4°C vs TRI-MIR 30.9 ± 0.4°C, not significant; and ADJ-IPS of 31.2 ± 0.2°C vs ADJ-MIR of 31.2 ± 0.2°C, not significant).

Immediately after gangliolysis, trigger zones were completely abolished and all thresholds were elevated in the treated divisions. No systematic changes were found after the two microvascular decompressions. The results were not subjected to statistical analysis because of the small number of patients tested.

COMMENT

On routine examination, when crude sensory tests are employed, observations of hypalgesia and hypesthesia are infrequent in ITN.[3,20] When more sophisticated and quantitated methods are used, small-scale sensory abnormalities may become apparent. In this study, raised thresholds were found both in the affected divisions and the nonsymptomatic contiguous divisions, indicating involvement of the nearby "silent" branch, too. Sensory functions subserved by both large- and small-diameter fibers were affected. The numerous reports of trigeminal root indentation or distortion by a vascular loop or similar structure, witnessed at operation,[5,7,21] provide a reasonable explanation for these findings. Whether they bear any causal relationship to ITN will be discussed below.

According to the study design, each patient served as his/her own control. The importance of using the patient's healthy side for comparison is underscored by two recent studies by Leandri and coworkers assessing somatosensory evoked potentials in ITN.[11,12] When early scalp responses evoked by the stimulation of both infraorbital nerves were compared between sides, delays of conduction were found on the painful side in nine of 38 cases.[11] When the authors performed only unilateral recordings, they could not detect significant deviations from normal values.[12]

One might dismiss the results of the present study as coincidental and due to patient expectation or the masking effect of trigeminal pain. In light of the used techniques, this seems highly unlikely. The patients were tested when at least 30 minutes from the last attack had elapsed. Thermal stimuli never caused pain paroxysms in the patients; yet just these thresholds were quite often abnormal. Threshold alterations were also more frequently present in the nonsymptomatic adjacent divisions where testing is not likely to be negatively affected by poor patient cooperation. The interpretation of results is not hampered by overlapping of dermatomes, either; there is very little functional overlap between the three trigeminal dermatomes.[29] The results are best explained by a lesion somewhere along the trigeminal afferent pathway, probably in the presynaptic part,[11] affecting not only those fibers innervating the painful division but the adjacent division as well. The discrepancy among the locations of pain, trigger zones, and sensory deficits does not confound the issue. In fact, it may offer an additional clue to the pathogenesis of ITN.

In a recent study,[26] Nurmikko and Bowsher reported on 12 patients with ophthalmic postherpetic neuralgia, half of whom suffered from severe touch-evoked pain (mechanical allodynia) in the maxillary division. Two aspects of this finding were discussed: expansion of the sensory dysfunction outside the originally affected division and pain caused by activation of nonnociceptive low-threshold mechanoreceptors. The authors concluded that their observations were clinical examples of the alterations in the central nervous system physiological mechanisms, known to take place in animals, after peripheral nerve unjury.[30] Deafferentation results in second-order neurons beginning to respond to stimuli from other than the usual anatomic areas. The expansion of the receptive fields is likely to include changes in the domain of sensory quality, too, so that neurons formerly responding to noxious stimuli start responding to other stimuli, such as tactile.[31] The resemblance between postherpetic neuralgia and ITN in this respect is evident. In each condition, there is evidence of mechanical allodynia (presenting as trigger zones in ITN) and a more widespread sensory dysfunction than the patient's pain description suggests. Although there are qualitative and quantitative differences, they may simply reflect the difference in the degree of peripheral nerve injury, which in ITN is minor and in postherpetic neuralgia is major. Perhaps the sensory abnormalities in ITN represent the primary lesion to the nerve or root. The trigger zones and pain paroxysms might then reflect various central alterations in the brain-stem trigeminal complex, as suggested previously.[9,19]

Some patients with ITN have a history of ipsilateral nonparoxysmal trigeminal pain weeks, months, or years before classic pain paroxysms develop.[32] Mitchell[33] noted that the typical ITN pains often spread to involve an adjacent division of the trigeminal nerve. Pretrigeminal neuralgia may, therefore, represent the first clinical manifestation of the neuropathic process that slowly, in a selected group of patients, leads to ITN. Accurate neurophysiological measurements at this early stage of the condition might elucidate the nature of the involvement of the trigeminal afferent pathways before the genesis of tic pain.

The findings of the present study are interpreted as further support for the hypothesis of combined peripheral and central pathophysiological mechanisms operant in ITN.[9,19,20] A lesion in the trigeminal nerve or root will result not only in sensory loss but also in functional changes of the receptive fields of the second-order neurons in the brain-stem trigeminal complex. As pointed out by Fromm and coworkers,[19] there is also pharmacological evidence of a failure of segmental inhibition in the trigeminal nucleus. The trigger zones (and pain paroxysms) presumably reflect these central alterations rather than the peripheral injury.

The reason for the predilection of the second and third divisions in the fully developed syndrome is obscure.[18,24] Some authors have attempted to account for it by drawing attention to the anatomy of the trigeminal nerve. Kerr[1] has proposed a permanent pulsatile contact of the carotid artery with the ventral surface of the gasserian ganglion, where mainly the second and third divisions are likely to be involved, because the first division is located farthest from the artery.[1] Jannetta[7] has reported compression of the superomedial aspect of the nerve root by the superior cerebellar artery in patients with pain in the second and third divisions, while the anteroinferior cerebellar artery seems to compress the inferior surface of the root in first division neuralgia cases.[7] According to the present study, however, no such accurate anatomical relationships are required to explain the locations of trigger zones and pain. Migration of trigger zones, mentioned by several authors before[1,4,5] and meticulously mapped by Dubner et al[9] in one patient with ITN, as well as the known tendency of the tic pain to disappear for long periods[2,4,20] militate against such a theory of simple local compression. A recent critical review of the subject also questions the significance of the microvascular decompression at the root level.[5] While the findings reported here add to the evidence of trigeminal pathway irritation or lesion (from any cause), some other unknown factor(s) leading to the development of ITN with its characteristic features must be inferred. The reason for the concentration of trigger zones in the central mask of the face cannot be explained adequately with available data, but is likely to lie in the complex interconnections of the neurons of the trigeminal nuclei, or even more rostrally.

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References

1. Kerr FWL. Craniofacial neuralgias. In: Bonica JJ, Liebeskind JC, Albe-Fessard DG, eds. *Advances in Pain Research and Therapy.* New York, NY: Raven Press; 1979;3:283-295.
2. Selby G. Diseases of the fifth cranial nerve. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. *Peripheral Neuropathy.* Philadelphia, Pa: WB Saunders Co; 1984:1224-1265.
3. Sweet WH. Percutaneous methods for the treatment of trigeminal neuralgia and other faciocephalic pain: comparison with microvascular decompression. *Semin Neurol.* 1988;8:272-279.
4. Terrence CF. Differential diagnosis of trigeminal neuralgia. In: Fromm GH, ed. *The Medical and Surgical Management of Trigeminal Neuralgia.* Mount Kisco, NY: Futura Publishing Co Inc; 1987:43-60.
5. Adams CBT. Microvascular compression: an alternative view and hypothesis. *J Neurosurg.* 1989;57:1-12.
6. Lewy FH, Grant FC. Physiopathologic and pathoanatomic aspects of major trigeminal neuralgia. *Arch Neurol Psychiatry.* 1938;40:1126-1134.
7. Jannetta PJ. Microsurgical approach to the trigeminal nerve for tic douloureux. In: Krayenbuhl H, Maspes PE, Sweet WH, eds. *Progress in*

Neurological Surgery: Pain—Its Neurosurgical Management. Basel, Switzerland: S Karger; 1976; 7:180-200.

8. Dyck PJ, Karnes J, O'Brien PC, Zimmermann IR. Detection thresholds of cutaneous sensation in humans. In: Dyck PJ, Thomas PK, Lambert EH, Bunge R, eds. *Peripheral Neuropathy.* Philadelphia, Pa: WB Saunders Co; 1984:1103-1138.

9. Dubner R, Sharav Y, Gracely RH, Price DD. Idiopathic trigeminal neuralgia: sensory features and pain mechanisms. *Pain.* 1987;31:23-33.

10. Stohr M, Petruch F, Scheglmann K. Somatosensory evoked potentials following trigeminal nerve stimulation in trigeminal neuralgia. *Ann Neurol.* 1981;9:63-66.

11. Leandri M, Parodi CI, Favale E. Early trigeminal evoked potentials in tumours of the base of the skull and trigeminal neuralgia. *Electroencephalogr Clin Neurophysiol.* 1988;71:114-124.

12. Leandri M, Campbell JA. Origin of early waves evoked by infraorbital nerve stimulation in man. *Electroencephalogr Clin Neurophysiol.* 1986; 65:13-19.

13. Cruccu G, Inghilleri M, Meglio M. Intracranial stimulation of the trigeminal nerve in man, III: sensory potentials. *J Neurol Neurosurg Psychiatry.* 1987;50:1323-1330.

14. Kimura J, Rodnitzky RL, Van Allen MW. Electrodiagnostic study of trigeminal nerve. *Neurology.* 1970;20:574-583.

15. Smith MC. Discussion on facial pain. *Proc R Soc Med.* 1954;47:783-789.

16. Beaver DL. Electron microscopy of the gasserian ganglion in trigeminal neuralgia. *J Neurosurg.* 1967;26:138-150.

17. Kerr FWL. Pathology of trigeminal neuralgia: light and electron microscopic observations. *J Neurosurg.* 1967;26:151-156.

18. Kugelberg E, Lindblom U. The mechanism of the pain in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry.* 1959;22:36-43.

19. Fromm GH, Terrence DF, Maroon JC. Trigeminal neuralgia: current concepts regarding etiology and pathogenesis. *Arch Neurol.* 1984; 41:1204-1207.

20. Loeser JD. Tic douloureux and atypical facial pain. In: Wall PD, Melzack R, eds. *Textbook of Pain.* Edinburgh, Scotland: Churchill Livingstone, 1989;535-543.

21. Richards P, Shawdon H, Illingworth R. Operative findings on microsurgical exploration of the cerebello-pontine angle in trigeminal neuralgia. *J Neurol Neurosurg Psychiatry.* 1983;46: 1098-1101.

22. Fraioli F, Esposito V, Guidetti B, Cruccu G, Manfredi M. Treatment of trigeminal neuralgia by thermocoagulation, glycerolisation and percutaneous compression of the Gasserian ganglion and/or retrogasserian rootlets: long-term results and therapeutic protocol. *Neurosurgery.* 1989;24: 239-245.

23. Zakrzewska JM. Cryotherapy in the management of paroxysmal trigeminal neuralgia. *J Neurol Neurosurg Psychiatry.* 1987;50:485-487.

24. Henderson WR. Trigeminal neuralgia: the pain and its treatment. *BMJ.* 1967;1:7-15.

25. Fruhstorfer H, Lindblom U, Schmidt WG. Method for quantitative estimation of thermal thresholds in patients. *J Neurol Neurosurg Psychiatry.* 1976;39:1071-1075.

26. Nurmikko T, Bowsher D. Somatosensory findings in postherpetic neuralgia. *J Neurol Neurosurg Psychiatry.* 1990;53:135-141.

27. Louis DS, Greene TL, Jacobson KE, Rasmussen C, Kolowich P, Goldstein SA. Evaluation of normal values for stationary and moving two-point discrimination in the hand. *J Hand Surg.* 1984;9A:552-555.

28. Kirk RE. *Experimental Design: Procedures for the Behavioral Sciences.* Belmont, Calif: Brooks/Cole; 1968:69-98.

29. Fromm GH. Anatomy and physiology of the trigeminal system. In: Fromm, GH, ed. *The Medical and Surgical Management of Trigeminal Neuralgia.* Mount Kisco, NY: Futura Publishing Co Inc; 1987:17-30.

30. Wall PD, Fitzgerald M, Nussbaumer JC, Van der Loos H, Devor M. Somatotopic maps are disorganized in adult rodents treated neonatally with capsaicin. *Nature.* 1982;295:691-693.

31. Devor M. Central changes mediating neuropathic pain. In: Dubner R, Gebhart GF, Bond MR, eds. *Proceedings of the Fifth World Congress on Pain,* Amsterdam, the Netherlands: Elsevier; 1988:114-128.

32. Fromm GH, Graff-Radford SB, Terrence CF. Pre-trigeminal neuralgia. *Neurology.* 1990;40: 1493-1495.

33. Mitchell RG. Pre-trigeminal neuralgia. *Br Dent J.* 1980;149:167-170.

Neurophysiologic Studies of the Peripheral Nervous System in Nephropathic Cystinosis

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• Cystinosis is an autosomal recessive metabolic disorder in which nonprotein cystine accumulates within most body tissues due to a defect in lysosomal cystine transport. Neurologic declarations are only recently being recognized. We studied 13 cystinotic subjects (aged 5 to 21 years old), determining median motor and sensory nerve conduction velocities, F waves, peroneal motor nerve conduction velocities, sural sensory nerve conduction velocities, median sympathetic skin response, electrocardiogram R-to-R variability, and blink reflex analysis. The results were normal. We conclude that neurophysiologic testing suggests relative sparing of the peripheral nervous system in nephropathic cystinosis.

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Cystinosis is an autosomal recessive metabolic disorder in which nonprotein cystine accumulates within most body tissues.[1] The cystine accumulates within the lysosomes of cells due to a defect in lysosomal cystine transport.[2] Cystinosis can be divided into two major clinical groups, nephropathic and benign. Nephropathic cystinosis can be further divided into infantile and late-onset (juvenile or adolescent) forms. The infantile form is the most common, and the most devastating. Systemic complications include renal Fanconi syndrome with rickets, growth retardation, and renal failure that necessitates renal transplantation by an average age of 10 years. Children with infantile cystinosis are now surviving to the second and third decade of life, permitting evaluation of the long-term effects of cystinosis on nonrenal tissues. While patients with cystinosis had been believed to have normal neurologic function, recent evidence suggests that there may be central nervous system involvement. Neurologic abnormalities that have been described include confusion and short-term memory loss, rigidity, myopathy, tremor, gait apraxia, generalized hypotonia, intention tremor, mild diffuse hyperreflexia, speech difficulties, slowed saccades, decreased corneal sensitivity, abnormal visual contrast sensitivity, and enhancement of the photic-induced sneeze reflex.[3-13] We performed studies of the peripheral nervous system in patients with nephropathic cystinosis to determine if the pathophysiologic mechanisms that result in central nervous system dysfunction also affect the peripheral nervous system.

PATIENTS AND METHODS

We studied 13 patients with nephropathic cystinosis (aged 5 to 21 years old; 10 patients were male). All patients were examined neurologically. Ten of the 13 had poor gross and/or fine motor skills for their age. Seven of the 13 exhibited generalized hypotonia in the face of normal or brisk deep tendon reflexes. Five of the 13 were borderline or frankly microcephalic. None showed evidence of peripheral neuropathy or neuromuscular dysfunction. No patient had any other systemic disease known to affect the neuromuscular system. Eleven patients had been receiving long-term oral cysteamine therapy. One patient had been taking cysteamine intermittently, and one patient had never received cysteamine therapy. Only the latter two patients had undergone renal transplantation.

For median motor nerve conduction velocities, an active electrode was placed over the thenar motor point with a reference distally on digit 1 and ground on the dorsal hand. The median nerve was stimulated at the wrist and elbow. Amplitude was measured from baseline to electronegative peak, and distal latency from shock artifact to onset of the electronegative potential. Distance was measured with a flexible cloth tape. F waves were elicited by stimulation of the median nerve at the wrist with anode distal to cathode. The shortest onset latency of eight F waves was recorded.

Peroneal motor nerve conduction velocities were determined with an active electrode over the center of the extensor digitorum brevis, and the reference electrode on digit 5; ground was over the dorsal aspect of the foot. Stimulation was applied at the ankle and at the fibular neck. Amplitudes, latencies, conduction velocities, and F waves were calculated as above. F waves were measured as the shortest onset of eight responses from the ankle.

Sural sensory nerve conduction velocities were recorded from a block electrode behind the lateral maleolus, and stimulation of the sural nerve was recorded 14 cm proximally. The best of four responses was taken; signal averaging was employed when necessary with eight to 16 sweeps. Latencies to electronegative onset and peak were determined. Amplitudes were measured from baseline to electronegative peak. Limb skin temperature was controlled at 34°C with an automatic feedback thermistor controlled heat lamp (Dantec Model 15H02). One-centimeter tin disk electrodes were used throughout.

Median sympathetic skin responses were determined by placing an active electrode on the palm, reference, and ground on the dorsum of the hand. Responses were recorded after stimulation of the median nerve at the wrist, ipsilaterally. Median sympathetic skin response amplitude and latency to onset were measured.

R-R variability was determined by record-

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ing the electrocardiogram. The R-R range of 10 cycles was determined during normal tidal respiration, and again during one deep inspiration with Valsalva maneuver. The ratio of these two ranges was recorded. Two trials were taken from each subject, in the recumbent position.

Blink reflexes were recorded in four subjects. The active electrode was placed at the inferior orbital rim below the outer canthus. Stimulation at the supraorbital notch was achieved with a constant current stimulator. R1 and R2 responses, both ipsilateral and contralateral, were recorded after 10 trials at each site.

RESULTS

In all subjects, peripheral nerve conduction velocities and compound motor action potentials fell within the normal range for age (Table 1). The electrocardiogram R-to-R variability in 11 cystinotic subjects was normal. Blink reflexes could only be obtained in four subjects; all showed normal latencies (Table 2).

Table 1.—Peripheral Nerve Conduction Studies in Nephropathic Cystinosis*

Study	n	Mean (SD)	Range
Median motor amplitude, mV	11	6.5 (2.57)	2.8-11.5
Median motor distal latency, msec	11	2.6 (0.42)	1.9-3.5
Median motor conduction velocity, m/sec	11	54.5 (2.80)	50.0-58.6
Median motor F response, msec	8	19.5 (1.77)	17.0-22.0
Peroneal motor amplitude, mV	12	3.9 (2.68)	0.5-8.5
Peroneal motor conduction velocity, m/sec	12	53.5 (5.09)	46.3-65.5
Peroneal motor F response, msec	5	27.4 (5.94)	19.0-35.0
Sural sensory amplitude, μV	12	17.0 (5.22)	8.0-26.0
Sural sensory conduction velocity, m/sec	12	53.3 (5.22)	46.7-63.6
MSSR, mV	11	0.6 (0.48)	0.1-1.6
MSSR latency onset, msec	11	1.5 (0.28)	1.0-2.0

*MSSR indicates median sympathetic skin response.

Table 2.—Blink Reflex Latencies in Nephropathic Cystinosis*

Side Stimulated	Wave	n	Mean (SD)	Range
Right	R1	4	10.5 (0.71)	10.0-11.5
Right	R2 ipsilateral	4	29.3 (7.37)	22.0-37.0
Right	R2 contralateral	4	30.0 (6.27)	22.0-35.0
Left	R1	3	10.8 (0.29)	10.5-11.0
Left	R2 ipsilateral	4	28.4 (7.25)	21.0-36.0
Left	R2 contralateral	3	30.3 (8.08)	21.0-35.0

*The blink reflex latencies are given in milliseconds.

COMMENT

Autopsy studies have shown central nervous system pathologic findings in patients with cystinosis. There may be high parenchymal levels of cystine,[3,10] accumulations of cystine crystals within the choroid plexus, pineal gland, and meninges,[10] and extensive demyelination of the internal capsule and brachium pontis.[11] Results of previously reported electromyography demonstrate low amplitude, polyphasic motor-unit potentials of brief duration.[12] Muscle biopsy specimens have demonstrated variations in fiber size, atrophy of type I fibers, and numerous ring fibers, suggesting an underlying myopathy.[12] A recent report of neurologic complications in long-standing nephropathic cystinosis found no signs of peripheral nervous system dysfunction in 14 patients examined, although 93% (13/14) showed either clinical or neuroradiologic abnormality of their central nervous system.[13] To the best of our knowledge, pathologic findings in peripheral nerves in patients with cystinosis have not been described.

We found cystinosis patients to have normal nerve conduction velocities, electrocardiogram R-to-R variability, and blink reflex latencies. Nephropathic cystinosis appears to spare the neural mechanisms involved in these electrophysiologic tests.

Two interesting findings were the relative intolerance to blink reflex testing found in many of the subjects, and the precipitation of a sneeze following supraorbital nerve stimulation in two of the four patients who tolerated testing. Patients with cystinosis have an increased prevalence of the photic-induced sneeze reflex.[8,9] The photic-induced sneeze reflex is believed to be caused by optic-trigeminal summation or optic nerve-enhanced irritability of the trigeminal nerve.[8,9] Patients with cystinosis may have an underlying irritability of the trigeminal nerve, declared clinically as an increased prevalence of photic or supraorbital nerve stimulation-precipitated sneeze. Patients with cystinosis have been reported to show trigeminal dysfunction[7-9]

Most patients with cystinosis would be expected to show grossly normal neurologic function, moderate generalized hypotonia in the presence of normal or even brisk deep tendon reflexes, and gross and fine motor incoordination. A smaller than average head circumference is also common. Our neurophysiologic studies suggest that the peripheral nervous system is relatively spared in nephropathic cystinosis. Peripheral nerve electrophysiologic studies are, however, only a gross measure of peripheral nerve function. There may be subtle peripheral changes not apparent when employing our techniques. Further neuropathologic evaluation of the peripheral nervous system in nephropathic cystinosis may reveal abnormalities not apparent on clinical neurophysiologic evaluation.

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References

1. Gahl WA, Thoene JG, Schneider JA, O'Regan S, Kaiser-Kupfer MI, Kuwabara T. Cystinosis: progress in a prototypic disease. *Ann Intern Med.* 1988;109:557-569.

2. Jonas AJ, Smith MD, Schneider JA. ATP-dependent lysosomal cystine efflux is defective in cystinosis. *J Biol Chem.* 1982;257:13 185-13 188.

3. Jonas AJ, Conley SB, Marshall R, Johnson RA, Marks M, Rosenberg H. Nephropathic cystinosis with central nervous system involvement. *Am J Med.* 1987;83:966-970.

4. Trauner DA, Chase C, Scheller J, Katz B, Schneider JA. Neurologic and cognitive deficits in children with cystinosis. *J Pediatr.* 1988;112:912-914.

5. Gahl WA, Schneider JA, Thoene JG, Chesney R. Course of nephropathic cystinosis after age 10 years. *J Pediatr.* 1986;109:605-608.

6. Katz B, Melles RB, Schneider JA. Contrast sensitivity function in nephropathic cystinosis. *Arch Ophthalmol.* 1987;105:1667-1669.

7. Katz B, Melles RB, Schneider JA. Corneal sensitivity in nephropathic cystinosis. *Am J Ophthalmol.* 1987;104:413-416.

8. Katz B. Neuro-ophthalmologic manifestations of nephropathic cystinosis. In: Smith JL, Katz RS, eds. *Neuro-ophthalmology Enters the Nineties.* Hialeah, Fla: Dutton Press; 1988:331-341.

9. Katz B, Melles RB, Swenson MR, Schneider JA. Photic sneeze reflex in nephropathic cystinosis. *Br J Ophthalmol.* 1990;74:706-708.

10. Koizumi F, Koeda T, Wakaki K. Cystinosis with marked atrophy of the kidneys and thyroid. *Acta Pathol Jpn.* 1985;35:145-155.

11. Levine S, Paparo G. Brain lesions in a case of cystinosis. *Acta Neuropathol.* 1982;57:217-220.

12. Gahl WA, Dalakas MC, Chen KTK, et al. Myopathy and cystine storage in muscles in a patient with nephropathic cystinosis. *N Engl J Med.* 1988;319:1461-1464.

13. Fink JK, Brouwers P, Barton N, et al. Neurologic complications in long-standing nephropathic cystinosis. *Arch Neurol.* 1989;46:543-548.

Clinical Issues Relating to the Diagnosis of Mild Dementia in a British Community Survey

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• Many epidemiologists base their diagnoses of dementia on scores on brief cognitive tests, but the border between normal aging and mild dementia is so poorly understood that simple demarcations cannot adequately encapsulate the wealth of clinical material that needs to be taken into account in assigning diagnostic labels. Data from a British study of the prevalence and natural history of dementia, in which diagnoses of dementia were made by clinicians using a new, standardized interview schedule, are presented to demonstrate the effects of physical disability, psychiatric illness, and other factors on memory impairment and performance in everyday life. Our purpose is not to insist that clinicians are always correct but rather to highlight the complexities involved and the need for investigators to be more open about the way in which they distinguish between physical, psychiatric, and cognitive infirmities.

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Prevalence rates for advanced dementia show a fair degree of uniformity from study to study but rates for mild dementia vary widely, largely because of differences in definition.[1] Community surveys have become so expensive that many researchers base their diagnoses on brief cognitive tests, but two major difficulties follow from this. First, simple tests that focus on orientation and general knowledge were devised for use in hospitals and fail to detect a substantial proportion of community-resident demented people who tend to be much less severely affected.[2] In addition, cognitively intact old people do badly on tests for many reasons, including poor concentration, low intelligence, deafness, aphasia, depression, and physical illness and many will be wrongly labeled as demented if diagnoses are based on test scores alone.[3,4]

Second, the *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition,* now defines dementia as a degree of cognitive impairment that is sufficient to interfere with social and occupational function.[5] This is important because demented persons cannot provide an accurate account of their own abilities so that independent evidence is required if the criteria are to be applied correctly. Clinicians take histories from relatives as a matter of course, but epidemiologists have been loathe to follow suit, partly for economic reasons and partly through fear that relatives will attribute forgetfulness and loss of mental sharpness to normal aging and fail to report these conditions.[6] Whether this occurs in practice, however, remains to be seen.

The concept of mild dementia is relatively new and few investigators have the time and the money to follow up subjects over lengthy periods. It comes as no surprise that clinical validity is less than perfect, although mistakes are frequently just as revealing as "correct hits." When Bergmann and colleagues[7] traced subjects diagnosed as having mild or questionable dementia, six had died, three were clearly demented, and seven had improved but, significantly, four of the seven appeared to have been of lower than average intelligence in earlier life. In another British study, only six of 12 persons diagnosed as having mild organic impairment using the Geriatric Mental State Examination were judged to be demented 1 year later. Of the remainder, two were depressed, one had developed schizophrenia, and three were classified as normal.[8]

Clearly, low intelligence and functional psychiatric disorders obscure the clinical picture. This analysis seeks to unravel the effects of these and other factors using data from a longitudinal study in Cambridge, England, in which dementia was diagnosed using a comprehensive, standardized interview schedule, and operational criteria. We describe the clinical characteristics that persuaded psychiatrists to diagnose dementia in the absence of marked cognitive or behavioral deficits or to pass as normal individuals whose performance was consistent with dementia, with a view to highlighting important features that might be overlooked in surveys based on simple measures of cognitive function.

SUBJECTS AND METHODS

Patients aged 75 years and older on April 1, 1986, who were registered with six Cam-

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bridge general practices were screened over a 12-month period by trained lay interviewers who administered the Mini-Mental State Examination[9]; findings from a seventh practice have been excluded because the test was administered in a slightly different way and the results are not directly comparable. Patients who scored 23 or less of a maximum score of 30 points, together with a one in three sample of those who scored 24 or 25 points, were then assessed by psychiatrists using the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX).[10] The CAMDEX is a lengthy, structured interview that comprises a mental state examination, detailed cognitive tests, a medical and psychiatric history, a physical examination, and an interview with an informant (usually the closest relative) that inquires about changes in memory, intellect, and behavior and the duration and course of symptoms.

The CAMDEX incorporates criteria for dementia, delirium, and major depressive disorders. Diagnoses of dementia were based on the total clinical picture and required (1) a failure in performance in everyday activities, not due to physical illness or handicap, (2) an impairment of memory, and (3) a deterioration of personality or general intellectual capacity or disturbance of higher cortical function. Criteria for mild dementia included "difficulty in recalling recent information; limited or patchy disorientation to time and place; impaired problem solving, reasoning, and capacity to manage everyday activities, and diminished clarity of speech." The CAMDEX also includes the category of minimal or questionable dementia. Minimally demented subjects, who failed to satisfy criteria for dementia proper, were described as having "a limited and variable impairment in recalling recent events; minor and variable errors in orientation; some blunting of reasoning and problem solving; and occasional errors in occupational tasks."

The analysis examines the scores of nondemented, minimally demented, and mildly demented subjects on two measures of memory and behavior taken from CAMDEX. Similar findings would doubtless emerge whatever indexes were used—the importance of the analysis lies in the level of agreement between subjects' broad positions on the scales and the judgments made by experienced clinicians. The memory scale comprised a series of short-term memory tests (recall of three words, a five-item name and address, and six photographs and recall of the photographs when presented later), which required that subjects be able to hear, to see the photographs, and to write a name and address on an envelope (missed items were scored as zero). The behavioral measure, the Blessed-Roth Dementia Scale, consists of questions put to informants about memory, orientation, and personal care.[11] Maximum scores on the memory tests and dementia scale were 20 and 34 points, respectively. The Blessed-Roth scale specifies that allowance be made for physical disabilities and illnesses that restrict activities[11] but, in this study, informants were asked about what subjects actually managed, not what they might have managed in different circumstances. For this reason, the Blessed-Roth Dementia Scale will be referred herein as the "disability scale."

The method used to highlight subjects who posed, or might have posed, diagnostic difficulties was simple. Scores on both scales were divided as closely as possible into the lowest third, an intermediate group, and the highest third, and the groups were then cross-tabulated. The majority of subjects occupied obvious positions; most mildly demented subjects, for example, performed badly on memory tests and their informants reported changes in memory, orientation, and personal care, but we focused on subjects who occupied anomalous or intermediate positions.

Demented subjects were reviewed 1 and 2 years later using the same procedures. Diagnoses were confirmed for all surviving moderately or severely demented cases, and for 63 of 67 surviving, mildly demented cases at 1 year and for 55 of 57 who were seen at 2 years.[12] Six of 29 minimally demented respondents who were reviewed at 1 year and 12 of 24 survivors who were reviewed at 2 years showed evidence of cognitive deterioration. However, the fact that 13 minimal cases were regraded as normal 1 year later suggests that diagnoses at this early stage have limited validity, at least under field conditions, and the results that follow concern the normal and mildly impaired groups. As our findings make clear, "normal" subjects were often far from normal in the usual sense but we used the term as shorthand for "nondemented" or "presumably nondemented."

RESULTS

Study Population

The response rate in the screening phase of the study was 90% (2311/2569); 196 patients refused to be seen, 48 could not be traced, and 14 were too ill to be interviewed. The response rate in the diagnostic phase was 82% (481/586); 68 eligible patients refused, 16 had died, and 21 could not be traced or were missed in error.[13] Relatives or other informants were interviewed for 89% (430/481) of the subjects assessed using CAMDEX; 13 had no surviving family, eight refused permission, three informants chatted informally but refused or were unable to answer every question, seven could not be contacted, and 20 lived too far away to be visited.

Complete information was available therefore for 182 subjects judged to be cognitively intact, for 40 minimally demented subjects, and for 91 mildly demented subjects (the remaining 117 subjects were moderately or severely demented). Table 1 shows that subjects were generally very old and that most were female. A larger proportion of normal subjects had worked in semiskilled or unskilled occupations because of bias in the screening test. As a result of this bias, working-class respondents were particularly likely to score below the specified cut-point, despite the fact that they were no more likely to be diagnosed as demented than those from more privileged backgrounds.[4,14]

Table 1.—Demographic Characteristics of Normal, Minimally, and Mildly Demented Subjects

	Normal, n=182	Minimal Dementia, n=40	Mild Dementia, n=91
Mean age	82.4	85.5	84.3
(SD)	(4.7)	(6.1)	(4.9)
Mean years of education	9.1	9.3	9.7
(SD)	(1.3)	(1.3)	(2.2)
Female, %	68	80	65
Social class, %*			
I, II	9	8	20
III	47	46	44
IV, V	44	46	36
Residence, %			
Community	86	83	88
Institution	14	17	12

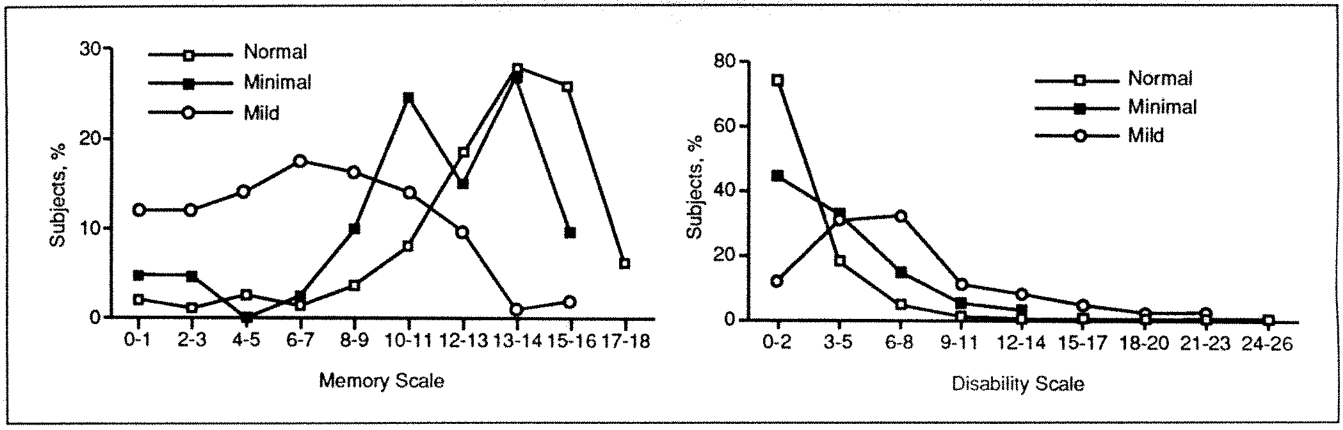
*Office of Population Censuses and Surveys criteria.[29]

Score Distributions

The Figure shows scores of normal, minimally demented, and mildly demented subjects on the memory and Blessed-Roth disability scales. Note that the scales work in opposite directions since active, mentally alert subjects should normally achieve high memory scores but low disability scores, while demented subjects should normally have low memory scores but higher disability scores. Memory scores covered a wide range and were generally high, while disability scores covered a narrower range and were generally low. Predictably, memory scores declined with advancing levels of dementia from a mean value of 13.5 (SD ± 3.8) for normal subjects to 11.0 (±4.0) for minimally demented subjects and 6.8 (±4.1) for mildly demented subjects (Kruskall-Wallis test, $P < .00005$). Conversely, disability scores increased from 1.9 (±3.0) to 3.5 (±3.1) and 6.8 (±4.2) for normal, minimally, and mildly demented subjects, respectively ($P < .00005$). Even so, there was a marked overlap in scores on both scales.

Diagnoses vs Test Scores

Table 2 lists the numbers of normal, minimally, and mildly demented subjects with high, intermediate, and low scores on the memory and Blessed-Roth disability scales. As expected, most normal subjects lie in the top



Scores on the memory and Blessed-Roth disability scales for normal, minimally, and mildly demented subjects.

left-hand corner of the table (good memory, low disability), while most mildly demented subjects lie in the bottom right-hand corner (poor memory, high disability). A simple classification system based on the three cells in the bottom right-hand corners performed surprisingly well in distinguishing between normal and minimally demented subjects on the one hand and mildly demented subjects on the other. Cells 6, 8, and 9 contain 91% (83/91) of the mildly demented group, while the remaining cells contain 84% (187/222) of the normal and minimally demented groups. However, as many as 30% (35/118) of subjects in cells 6, 8, and 9 were judged to be normal or minimally demented and the remainder of this section concerns respondents who occupy anomalous positions. For convenience, subjects have been divided into seven groups according to their positions in Table 2.

Table 2.—Distribution of Trisected Scores on the Memory and Blessed-Roth Disability Scales for Normal, Minimally, and Mildly Demented Subjects*

	Memory Scores								
	Normal, n=182			**Minimal Dementia, n=40**			**Mild Dementia, n=91**		
Blessed-Roth Disability Scores	**Good**	**Middle**	**Poor**	**Good**	**Middle**	**Poor**	**Good**	**Middle**	**Poor**
Low	59_1	38_2	15_3	2_1	5_2	6_3	$-_1$	1_2	2_3
Middle	20_4	22_5	11_6	3_4	10_5	3_6	$-_4$	3_5	18_6
High	6_7	8_8	3_9	1_7	3_8	7_9	2_7	14_8	51_9

*Cell numbers are subscripted. Minus signs indicate 0.

Group A

Twenty-two normal respondents had poor or intermediate memory scores and high or intermediate scores on the Blessed-Roth disability scale (cells 6, 8, or 9). Six had major depressive illnesses and seemed to do badly on testing because of poor concentration and motivation. Four of them gained points on the disability scale, not because of cognitive impairment, but because of their need for prompting and supervision and, in one case, because of urinary incontinence that had been present for many years following surgery.

Three respondents did badly on testing and needed help with everyday tasks because of blindness, deafness, aphasia, or physical incapacity. Of the remainder, two were delirious; one was mentally handicapped but continued to function at her usual low level; one was of limited intellect and had always needed help with shopping and paying bills, and two had chronic, relapsing manic-depressive psychoses. An elderly man who did badly on one memory test, but satisfactorily on the others, was described by his son as having great difficulty in recalling recent events. This was at odds with the psychiatrist's own assessment but, as the son had failed to visit his father for more than 1 year, his opinion was overruled. Finally, one profoundly deaf man looked vague and perplexed, did badly on testing, and was said by his wife to be forgetful and muddled. She retracted this later, claiming that he managed the garden and odd jobs around the house. This seemed highly implausible given his marked physical frailty, but his poor performance was attributed to deafness. In retrospect, however, he was almost certainly dementing.

Group B

Fifteen normal subjects did badly on testing, but received low disability scores (cell 3). There were obvious reasons for the discrepancy in 11 cases, including depression, chronic schizophrenia, blindness, deafness, terminal cancer, limited English, and illiteracy coupled with extreme anxiety. The psychiatrist considered the possibility of an amnestic disorder in the case of a difficult, uncooperative man with a long history of alcohol abuse but his daughter dismissed his forgetfulness as just another sign of his "lazy, good-for-nothing ways." Unfortunately, he died before he could be reviewed and his true status remains unknown. The five remaining subjects, who were described as being occasionally forgetful, were all bright and lively and perfectly capable of managing their own affairs.

Group C

Six normal old people did well on testing but had high disability scores (cell 7), usually because of physical infirmity. Three had had strokes, one was partially sighted and deaf, and two were ill but their informants denied any mental changes.

Group D

Twenty-two normal subjects scored in the middle range on both scales (cell 5). Six had difficulty completing the memory tests because of a physical handicap and received higher than average scores on the disability scale for the same reason. Another five were physically handicapped and depressed; one was delirious; one had an organic personality disorder following a stroke and one spoke so little English that she had difficulty understanding the questions put to her. Two women, who had always been clinging and dependent, became anxious on testing, refused to exert themselves, and simply gave up. The remaining five subjects were said to be occasionally forgetful but their lapses were of no practical consequence and they appeared to the interviewers to be bright, alert, and fully in touch with recent events.

Group E

One diabetic woman who was rated as mildly demented scored in the middle range on memory tests and had a low disability score (cell 3). This seems anomalous but she was also disoriented to time, and her daughter reported a 10-year history of gradually progressive apathy, withdrawal, and declining personal standards. However, when she was seen 1 year later, her insulin-dependent diabetes had come under better control, she was much more responsive, and she did better on testing. The psychiatrist reclassified her as minimally impaired but, in hindsight, her mental impairment had probably been exacerbated by hyperglycemia at the time of her first assessment.

Group F

Two mildly demented subjects received low disability scores (cell 3). One had a congenital deformity and had always been cared for by a younger sibling. The latter acknowledged a degree of forgetfulness and indecisiveness, but she explained these changes in physical terms, presumably out of habit. In the other case, a simple, poorly educated man denied that his wife had deteriorated despite the fact that she failed every memory test and could not recall what had happened earlier that day. He had gradually taken over responsibility of running the house but he enjoyed this so much and made so few demands of his spouse that he seemed genuinely not to notice what was apparent to the psychiatrist within a minute or two of meeting her.

Group G

The two seemingly mildly demented women who performed well on memory tests but received high disability scores were of particular interest (cell 7). One had a long history of depression and described a number of depressive symptoms, but the interviewer was struck by her inertia and perplexity, her disorientation to time, and her marked constructional dyspraxia. The nursing home officer who had known her for many years reported that she was difficult, demanding, and occasionally muddled in her thinking, but otherwise mentally intact. In retrospect, it seems highly likely, in view of her good performance on memory tests, that she was depressed with secondary cognitive impairment and that her dyspraxia was due to the focal effects of a small stroke sustained several years previously but, unfortunately, she moved away and could not be reviewed.

Important clinical features may have been missed in the case of another elderly woman who was judged to be demented despite her good performance on testing. She looked bewildered at the time of her first assessment, her speech was rambling and repetitive, and her daughter described fluctuating disorientation and confusion. She was profoundly demented 2 years later, but it was noticed when compiling this report that her symptoms had developed after a blow to her head, which raises the possibility of a chronic subdural hematoma. The interviewer was correct to attend to the informant's report of variable confusion but remiss in failing to attend to its practical implications.

COMMENT

The methods used to examine the impact of functional psychiatric illness, physical infirmity, and the perceptiveness of informants are contrived but, despite this, they serve to highlight a number of important points. Subjects rated as cognitively intact achieved significantly better scores on the average than mildly demented people, but the overlap in memory and behavioral scores was so marked that demarcations based on absolute levels of performance would have resulted in many erroneous diagnoses. The same applies to a rudimentary classification based on trisected scores. This worked much better than expected, bearing in mind that respondents who scored 26 points or more on the Mini-Mental State Examination were excluded together with those who were markedly demented but, even so, 30% of subjects whose scores fell within the relevant cells (cell 6, 8, or 9) failed to meet the criteria for mild dementia.

Berg and colleagues[16] have shown that mild dementia, and even very mild dementia, can be reliably and validly diagnosed in carefully selected hospital populations. As in our study, psychometric scores were of limited value in themselves,[15] but standardized ratings based on detailed assessments were in striking accord with autopsy findings.[16-18] Subjects with physical, neurologic, or psychiatric disorders were excluded from their studies[16-18] but epidemiologists are required to make a judgment in the case of every person seen and they frequently contend with difficult and confusing presentations.

Clinical assessments have the advantage that many different factors can be considered, but complex judgments based on subjects' backgrounds, social circumstances, and physical health open the way to low levels of interobserver reliability. The *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* and CAMDEX criteria have much in common; they specify the types and numbers of abnormalities required for diagnosis but they lack clear anchor points, and clinicians working in different centers might arrive at different interpretations.[19] Individual research teams can achieve high levels of agreement. The CAMDEX interviewers, for example, assigned identical diagnoses and severity levels in 20 of 23 joint interviews but, significantly, all three disagreements related to minimal and mild dementia.[20] Similarly, when a random selection of 20 CAMDEX schedules from each of the five severity ratings was rated blindly using the Clinical Dementia Rating scale,[21] the level of agreement was acceptably high at 75%. However, six of the 20 subjects who were classified as normal by CAMDEX were rated as questionably demented on the Clinical Dementia Rating Scale and two were rated as mildly demented.[20]

Premorbid ability, mood, motivation, sensory deficits, and physical incapacity must all be considered when attempting to distinguish between normal aging and mild dementia, although it is difficult to conceive of any system capable of distinguishing between the two with perfect reliability and validity in unselected populations. A dimensional view of dementia, which separates "cases" from "noncases," requires that failure to answer a question because of deafness, for example, be distinguished from failure due to organic mental disorder, but deafness and dementia both increase with age and many demented people are also deaf.[22] Clearly, the way in which this problem is resolved will determine who is and who is not classified as demented.

Informants' accounts were highly consistent with other independent measures of cognition and behavior and proved immensely helpful in making sense of complex cases.[23] Historical information is essential if people suffering from schizophrenia, amnestic disorders, delirium, and other disabilities are to be classified correctly but, clearly, small numbers of relatives provided misleading answers, usually through ignorance or emotional bias.[23] In addition, informants will sometimes minimize early mental changes or attribute them to laziness or awkwardness but, as before, these differences in sensitivity and attribution will be felt most keenly at the borderline between normal aging and mild cognitive impairment.

Dementia can also be seen as part of a continuum, in the sense that no clear boundaries exist between normal mental function; minor lapses of memory and judgment that are of no practical consequence, at least for the present; and early dementia. Scores on memory tests and behavioral ratings are smoothly and continuously distributed in representative samples[24] and the numbers of senile plaques and neurofibrillary tangles found at autopsy increase smoothly and continuously with advancing age.[25,26] Indeed, it seems likely that a sizable proportion of the normal subjects considered in this study, who had all scored 25 points or less on the Mini-Mental State Examination, had a greater than average number of plaques, tangles, infarctions, and other lesions for their age, but not in sufficient numbers to produce clinical decompensation.[27,28]

This is not to say that dementia does not exist. It does exist and efforts to diagnose dementia in its early stages will assume particular significance should pharmacologic treatments become available. The dividing line between normality and early dementia might prove to be considerably more fluid than expected, however, and clinical findings of the kind we presented will be of great importance if assessment procedures and diagnostic criteria are to be improved. Brief assessment procedures cannot do justice to the complex data that need to be considered and they provide so little information that researchers will have difficulty in tracing the factors responsible for diagnostic errors. Detailed clinical assessments, informant reports, prolonged follow-up, and the reporting of inconsistencies in presentation and outcome will be of great help in filling this vacuum.

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References

1. Mowry BJ, Burvill PW. A study of mild dementia in the community using a wide range of diagnostic criteria. *Br J Psychiatry*. 1988;153:328-34.

2. Fillenbaum GG. Comparison of two brief tests of organic brain impairment: the MSQ and the short portable MSQ. *J Am Geriatr Soc*. 1980; 28:381-384.

3. O'Connor DW, Pollitt PA, Hyde JB, et al. The reliability and validity of the Mini-Mental State in a British community survey. *J Psychiatr Res*. 1989;23:87-96.

4. O'Connor DW, Pollitt PA, Treasure FP, Brook CPB, Reiss BB. The influence of education, social class and sex on Mini-Mental State scores. *Psychol Med*. 1989;19:771-776.

5. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-Revised, Third Edition*. Washington, DC: American Psychiatric Association; 1987.

6. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. *JAMA*. 1989; 262:2551-2556.

7. Bergmann K, Kay DWK, Foster EM, McKechnie AA, Roth M. A follow-up study of randomly selected community residents to assess the effects of chronic brain syndrome and cerebrovascular disease. In: *Proceedings of the 5th World Congress of Psychiatry*. Princeton, NJ: Excerpta Medica; 1973:856-865.

8. Copeland JRM, McWilliam C, Dewey ME, et al. The early recognition of dementia in the elderly: a preliminary communication about a longitudinal study using the GMS (community version). *Int J Geriatr Psychiatry*. 1986;1:63-70.

9. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1985;12:189-198.

10. Roth M, Tym E, Mountjoy CQ, et al. CAMDEX: a standardised instrument for the diagnosis of mental disorder in the elderly with special reference to the early detection of dementia. *Br J Psychiatry*. 1986;149:698-709.

11. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and senile changes in the cerebral grey matter of elderly subjects. *Br J Psychiatry*. 1968;114:797-811.

12. O'Connor DW, Pollitt PA, Hyde JB, Fellowes JL, Miller ND, Roth M. A follow-up study of dementia diagnosed in the community using the Cambridge Mental Disorders of the Elderly Examination. *Acta Psychiatr Scand*. 1990;81:78-82.

13. O'Connor DW, Pollitt PA, Hyde JB, et al. The prevalence of dementia as measured by the Cambridge Mental Disorders of the Elderly Examination. *Acta Psychiatr Scand*. 1989;79:190-198.

14. O'Connor DW. The influence of education and social class on the diagnosis of dementia in a community population. *Psychol Med*. In press.

15. Storandt M, Hill RD. Very mild senile dementia of the Alzheimer type, II: psychometric test performance. *Arch Neurol*. 1989;46:383-386.

16. Berg L, Miller JP, Storandt M, et al. Mild senile dementia of the Alzheimer type, 2: longitudinal assessment. *Ann Neurol*. 1988;23:477-484.

17. Rubin EH, Morris JC, Grant EA, Vendegna T. Very mild senile dementia of the Alzheimer type, I: clinical assessment. *Arch Neurol*. 1989; 46:379-382.

18. Morris JC, McKeel DW, Fulling K, Torack RM, Berg L. Validation of clinical diagnostic criteria for Alzheimer's disease. *Ann Neurol*. 1988; 24:17-22.

19. Jorm AF, Henderson AS. Possible improvements to the diagnostic criteria for dementia in *DSM-III*. *Psychol Med*. 1985;147:394-399.

20. O'Connor DW. *The Prevalence of Dementia as Measured by CAMDEX*. Cambridge, England: University of Cambridge; 1990. Thesis.

21. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry*. 1982;140:566-572.

22. Herbst KG, Humphrey C. Hearing impairment and mental state in the elderly living at home. *BMJ*. 1980;281:903-905.

23. O'Connor DW, Pollitt PA, Brook CPB, Reiss BB. The validity of informant histories in a community study of dementia. *Int J Geriatr Psychiatry*. 1989;4:203-208.

24. Brayne C, Calloway P. Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? *Lancet*. 1988;1:1265-1267.

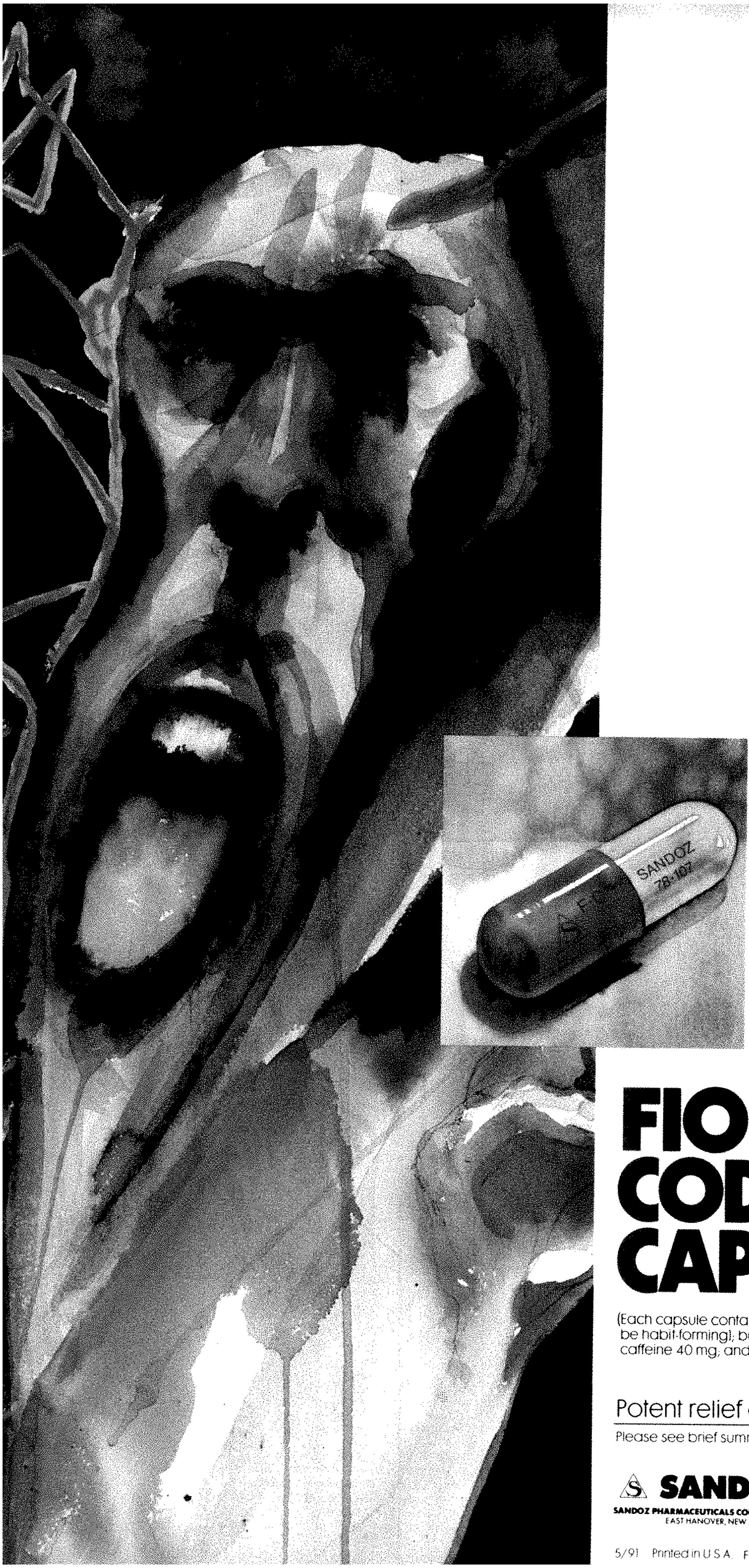
25. Matsuyama H. Incidence of neurofibrillary change, senile plaques, and granulovacuolar degeneration in aged individuals. In: Reisberg B, ed. *Alzheimer's Disease: the Standard Reference*. New York, NY: Free Press; 1983:149-154.

26. Miller FD, Hicks SP, D'Amato CJ, Landis JR. A descriptive study of neuritic plaques and neurofibrillary tangles in an autopsy population. *Am J Epidemiol*. 1984;120:331-341.

27. Katzman R, Aronson M, Fuld P, et al. Development of dementing illnesses in an 80-year old volunteer cohort. *Ann Neurol*. 1989;25:317-324.

28. Arendt T, Bigl V. Alzheimer's disease as a presumptive threshold phenomenon. *Neurobiol Aging*. 1987;8:552-554.

29. Office of Population Censuses and Surveys. *Classification of Occupations*. London, England: Her Majesty's Stationary Office; 1980.



HEADACHE DESCRIBED

"Headache"– a personal interpretation of headache pain by John Crowley, a headache patient.

HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL® WITH CODEINE CAPSULES Ⓒ III

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming], caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

SANDOZ

SANDOZ PHARMACEUTICALS CORPORATION
EAST HANOVER, NEW JERSEY 07936

5/91 Printed in U.S.A. FWC-1290-01

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE III CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming], butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: **General:** Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: **Commonly Observed:** The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse e reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fior with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated pati

The prescriber should be aware that these figures cannot be used to predict the incidence of side effe the course of usual medical practice where patient characteristics and other factors differ from those that pre in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other cl investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Place (N =
Central Nervous		
Drowsiness	2.4%	0.5
Dizziness/Lightheadedness	2.6%	0.5
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the prop of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who rep on at least one occasion, an adverse event of the type cited. All reported adverse events, except those a presented in the previous table, are included. It is important to emphasize that, although the adverse events re did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily c by Fiorinal® with Codeine

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infre is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All a events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been re since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal Codeine, are listed below. Many or most of these events may have no causal relationship with the drug an listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, u sciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastroint spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythr (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fi with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for pro periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Adminis and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the poten being abused. Psychological dependence, physical dependence, and tolerance may develop upon re administration and it should be prescribed and administered with the same degree of caution appropriate use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical depe may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the bar addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a bar is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur wi hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually d over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different wit regimens. One method involves initiating treatment at the patient's regular dosage level and gradually dec the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffein in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine over is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusi coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyp acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hypert hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restle tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorina Codeine. However, because strategies for the management of an overdose continually evolve, consultation regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codei the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are pres if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalini the urine, and correction of electrolyte disturbances should be accomplished through administration of intr fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hyp may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous inf severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be li Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

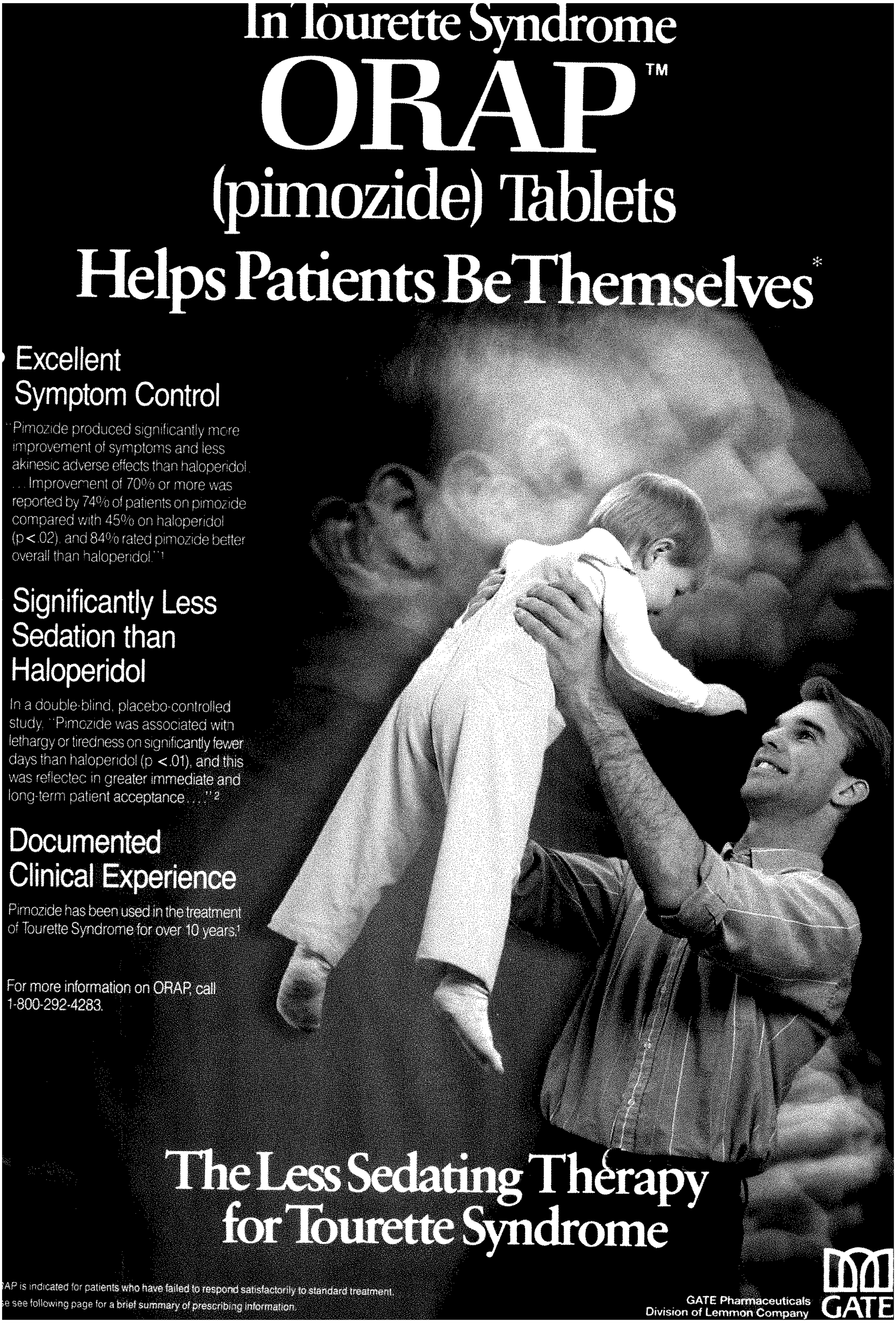
Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid o Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate respons achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should under continued surveillance and repeated doses of the antagonist should be administered as needed to adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant re or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

[NOVEMBER 1, 1990 FW



In Tourette Syndrome

ORAP™

(pimozide) Tablets

Helps Patients Be Themselves*

- **Excellent Symptom Control**

"Pimozide produced significantly more improvement of symptoms and less akinesic adverse effects than haloperidol. . . . Improvement of 70% or more was reported by 74% of patients on pimozide compared with 45% on haloperidol ($p < .02$), and 84% rated pimozide better overall than haloperidol."[1]

Significantly Less Sedation than Haloperidol

In a double-blind, placebo-controlled study, "Pimozide was associated with lethargy or tiredness on significantly fewer days than haloperidol ($p < .01$), and this was reflected in greater immediate and long-term patient acceptance. . . ."[2]

Documented Clinical Experience

Pimozide has been used in the treatment of Tourette Syndrome for over 10 years.[1]

For more information on ORAP, call
1-800-292-4283.

The Less Sedating Therapy
for Tourette Syndrome

AP is indicated for patients who have failed to respond satisfactorily to standard treatment.
e see following page for a brief summary of prescribing information.

GATE Pharmaceuticals
Division of Lemmon Company

GATE

ORAP™ The Less Sedating Therapy for Tourette Syndrome

(pimozide) Tablets

INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS)

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol.

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known.

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks.

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under "Tardive Dyskinesia" except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema
Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations
Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress
Endocrine: Loss of libido
Metabolic/Nutritional: Weight gain, weight loss
Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia
Psychiatric: Excitement
Skin: Rash, sweating, skin irritation
Special Senses: Blurred vision, cataracts
Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose.

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

Dispense in tight, light-resistant containers as defined in the official compendium.

Made in Canada

Manufactured by:
McNeil Pharmaceutical, (Canada) Ltd.
Stouffville, Ontario L4A 7x7

Printed in USA
Rev. A 6/88

GATE
GATE Pharmaceuticals
Division of Lemmon Company

1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

Cerebral Structure on Magnetic Resonance Imaging in Language- and Learning-Impaired Children

Terry L. Jernigan, PhD; John R. Hesselink, MD; Elizabeth Sowell; Paula A. Tallal, PhD

• Using magnetic resonance imaging 20 language- and learning-impaired children were compared with 12 normal control subjects. Gross brain structure was remarkably normal in the language- and learning-impaired group. Semiautomated morphometry was used to measure hemispheric volumes and cerebral asymmetries in six cerebral regions. The volume of the left posterior perisylvian region was significantly reduced in language- and learning-impaired children. Asymmetries in inferoanterior and superoposterior cerebral regions were also significantly different in this group. Results of descriptive group comparisons of estimated volumes of other cerebral gray-matter structures raise the possibility that some language- and learning-impaired children may have additional volume reductions in cortical and subcortical structures. The results suggest that hemispheric specialization of function may be anomalous in this population.

(*Arch Neurol.* 1991;48:539-545)

Developmental dysphasia is a specific disorder of language development of unknown etiology.[1] Because the disorder is not life-threatening, neuropathological examinations have been reported in only a few cases.[2,3] Neuropathological studies of dyslexia, a closely related developmental disorder of reading,[4,5] have led to hypotheses about its pathogenesis.[6] Symmetry of the planum temporale of the posterotemporal lobe, an unusual finding in normal subjects, was noted in all dyslexic patients examined in these studies. Also observed were frequent ectopias and dysplasias of the cortex. The planum symmetry appeared to be associated with larger right plana, rather than smaller left plana. It was hypothesized that injury to the brain during corticogenesis may lead to enhanced survival of right planum neurons, which produces anatomical symmetry and altered cerebral dominance.

With the recent advent of noninvasive, in vivo brain imaging methods, a few studies of dyslexia have been reported[7-10] (reviewed by Hynd and Semrud-Clikeman[11]). These imaging studies, employing several different measurement techniques, generally support neuropathological findings of unusual patterns of hemispheric asymmetry in dyslexic subjects. Of the new imaging techniques, magnetic resonance imaging (MRI) offers the most sensitive, noninvasive method for assessing brain structure during life and, as such, provides an unique opportunity for examining brain structure in children with specific developmental language disabilities.

In this study, MRI images from 20 language- and learning-impaired (L/LI) children and 12 matched control subjects were analyzed with semiautomated brain morphometry. Estimated volumes were obtained of cerebral regions and individual gray-matter structures. Based on previous findings with dyslexic children, specific analyses were developed to determine whether L/LI children would show anomalous asymmetries relative to controls.

SUBJECTS AND METHODS

The sample studied was drawn from a larger sample of 95 specifically language-impaired children and 60 age-, IQ-, race-, and socioeconomic status–matched controls, identified at the age of 4 years and studied longitudinally until the age of 8 years. Inclusion in the longitudinal study at the age of 4 years was based on the following criteria for both groups: (1) performance IQ of 85 or greater; (2) normal hearing acuity, no motor handicaps, and no oral, structural, or motor impairments affecting nonspeech movement of the articulators; (3) an English language background without significant dialectical or language differences in the home environment; (4) no obvious signs of infantile autism (as defined by *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*[12]); and (5) no known neurological disorders. Language-impaired children were at least 1 year behind chronological and nonverbal mental age on a battery of standardized receptive and expressive language measures. Normal control children met the same criteria as the language-impaired subjects except that their speech and language skills had to be within 6 months of their chronological age.

A subset of children who completed all 5 years of testing in the longitudinal study were selected to participate in this study. Twenty-eight children who continued to demonstrate significant language impairment as well as academic achievement deficits were selected as L/LI subjects. These subjects were selected initially based on their language impairment at the age of 4 years. At the time of this imaging study, when they had an average age of 9 years, they continued to be language impaired, but in addition, many had severe learning disabilities that emerged during the longitudinal study. For this reason, these subjects have been classified as L/LI. They may or may not be the same as those children selected based solely on reading ability (ie, developmental dyslexics), although they all did have severe reading impairment when MRI scanning was performed. Fourteen matched controls who demonstrated normal language development and academic achievement (reading, spelling, and mathematics) also agreed to participate.

Eight of the L/LI children and two of the controls were unable to complete the procedure, or the magnetic resonance images were

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technically inadequate for analysis owing to motion artifact. Thus, 20 L/LI children (13 boys and seven girls) and 12 control children (eight boys and four girls), aged 8 to 10 years, were studied. Table 1 summarizes the subjects' characteristics. The groups remained well matched for age and sex; however, the controls had a somewhat higher mean performance IQ. Seventeen of the L/LI children had Wechsler Intelligence Scale for Children performance IQs greater than 80. The remaining three had performance IQs of 75, 73, and 64 (demonstrating a decrease from their previous performance IQs as measured at the age of 4 years). Also, at the time of MRI scanning, all L/LI children lagged 2 years behind chronological age on the Curtiss-Yamada Comprehensive Language Evaluation Expressive or Receptive scales, except for one child who lagged 1 year behind on both scales, but had mathematics and vocabulary percentile scores of 0.

All but three children (two L/LI, one control) were right-handed. Because of concern about altered cerebral organization and symmetry in the left-handers, all analyses were conducted with and without these subjects. Both sets of results are given below, although they were virtually identical.

Table 1.—Subject Characteristics*

	Control	L/LI
No. of subjects	12 (11)	20 (18)
Sex, F/M	4/8 (3/8)	7/13 (6/12)
Handedness, L/R	1/11 (11)	2/18 (18)
Age, y, mean ± SD	9.0 ± 0.7 (8.9 ± 0.7)	8.9 ± 0.7 (9.0 ± 0.7)
WISC PIQ, mean ± SD	109 ± 14 (110 ± 14)	97 ± 16 (98 ± 16)
CYCLE age levels, mean ± SD		
Expressive	8.3 ± 1.4 (8.2 ± 1.5)	4.8 ± 1.2 (4.7 ± 1.3)
Receptive	8.3 ± 1.0 (8.4 ± 0.9)	5.3 ± 1.4 (5.3 ± 1.4)

*Results omitting left-handed subjects are given in parentheses. L/LI indicates language and learning impaired; WISC PIQ, Wechsler Intelligence Scale for Children Performance IQ; and CYCLE, Curtiss-Yamada Comprehensive Language Evaluation. CYCLE age levels are equivalents at 8-year-old testing. One L/LI subject who did not complete the WISC testing is omitted from the calculation of PIQ; his Leiter IQ was 118 less than 1 year before scanning.

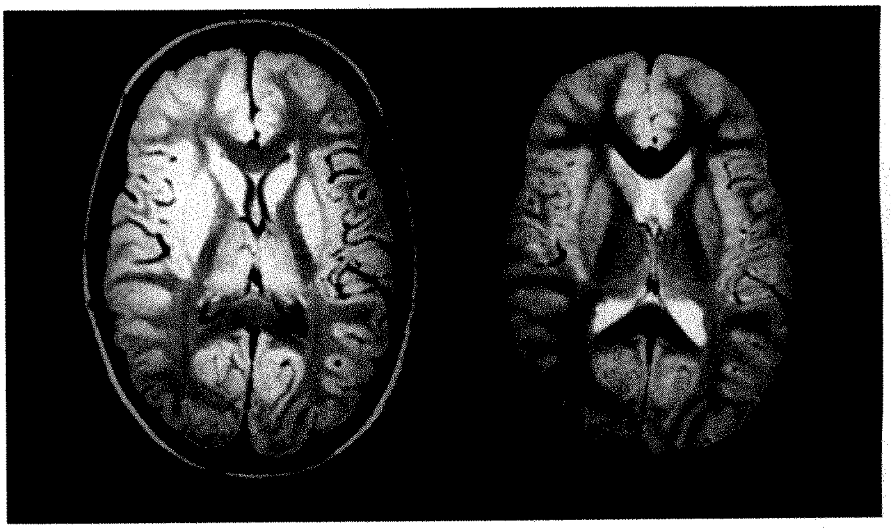

Fig 1.—Representative images from the standard protocol. Left, Repetition time, 2000 milliseconds; echo time, 25 milliseconds (proton density–weighted in text). Right, Repetition time, 2000 milliseconds; echo time, 70 milliseconds (T_2-weighted in text). Sections are 5 mm thick, with 2.5-mm gaps between images. A 24-cm field of view was used, and the matrix was 256 × 256.

MRI Protocol

Magnetic resonance imaging was performed with a 1.5-T superconducting magnet (Signa; General Electric, Milwaukee, Wis) at the University of California, San Diego/AMI Magnetic Resonance Institute. Proton density–weighted and T_2-weighted images (Fig 1) were obtained simultaneously for each section, using an asymmetrical, multiple-echo sequence (repetition time, 2000 milliseconds; echo time, 25, 70 milliseconds) to obtain images of the entire brain in the axial plane. Section thickness was 5 mm, with a 2.5-mm gap between successive sections in all instances. A 256 × 256 matrix and 24-cm field of view were used. Thus, a voxel measured $0.9375 \times 0.9375 \times 5$ mm, subtending a volume of 4.39 mm^3. No sedation was used during these examinations. Informed consent and full cooperation were obtained from all of the children and their parents.

MRI Analysis

The primary goal of the image-analytic methods was to define a region that would include those posterior perisylvian cortical structures of the temporal and parietal lobes that were deemed most relevant for the affected language functions, and to ensure that this region would have consistent boundaries from one subject to the next. Of secondary interest were other regions, including such cortical structures as the anterior language areas in insular cortex and superior parietal association cortex. Finally, for the purpose of exploratory analyses, major subcortical structures were also examined.

The visual identification of specific structures in magnetic resonance images is possible because of the tissue contrast between the gray-matter structures and the surrounding white matter or cerebrospinal fluid (CSF). However, measurements of volumes of cerebral structures must overcome several problems. First, because of partial voluming of gray matter, white matter, and CSF (or all three) at the edges of structures, definite edges are not always present. This allows considerable scope for variability in subjective determinations of such boundaries, for example, when tracing methods are used, leading to measurement unreliability in the computed volumes.

Visual determination of specific cortical structures on MRI depends on the presence of visible gross structural features relative to which the boundaries of the cortical regions can be defined. Standard regional divisions for the cortex are largely based on cortical gyral patterns, but the accurate localization of particular gyri or sulci, throughout a series of images, is often impossible. Furthermore, some boundaries, such as that between posterotemporal and inferoparietal cortex, are not clearly defined in gross structural terms (Fig 2). Also, even when attempts are made to standardize head positioning, head rotation (relative to the imaging plane) occurs in all three planes. This is especially true with unsedated subjects who must be sufficiently comfortable in position to avoid movement during the imaging session. Careful inspection indicates that small rotations substantially change the appearance of brain structures in the image plane, further complicating their visual identification; in addition, such rotations lead to spurious within-plane asymmetries of apparently comparable structures in the two hemispheres. Thus, manually tracing the structures in the sections where they are best visualized often leads to inaccurate volume and asymmetry assessments. The following techniques are designed to address each of these difficulties.

To facilitate and standardize the determination of structural edges, the present method involves a semiautomated classification of all pixels in the images based on their signal characteristics on the two original images of each section. A detailed description of the basic image analysis method has been reported elsewhere.[13] Only a brief summary is provided herein. For each axial brain section imaged, a computed matrix is produced. In this matrix, voxels are classified as most resembling (in signal strength) gray matter, white matter, CSF, or signal hyperintensities (tissue abnormalities). The full series of axial images is analyzed, beginning at the

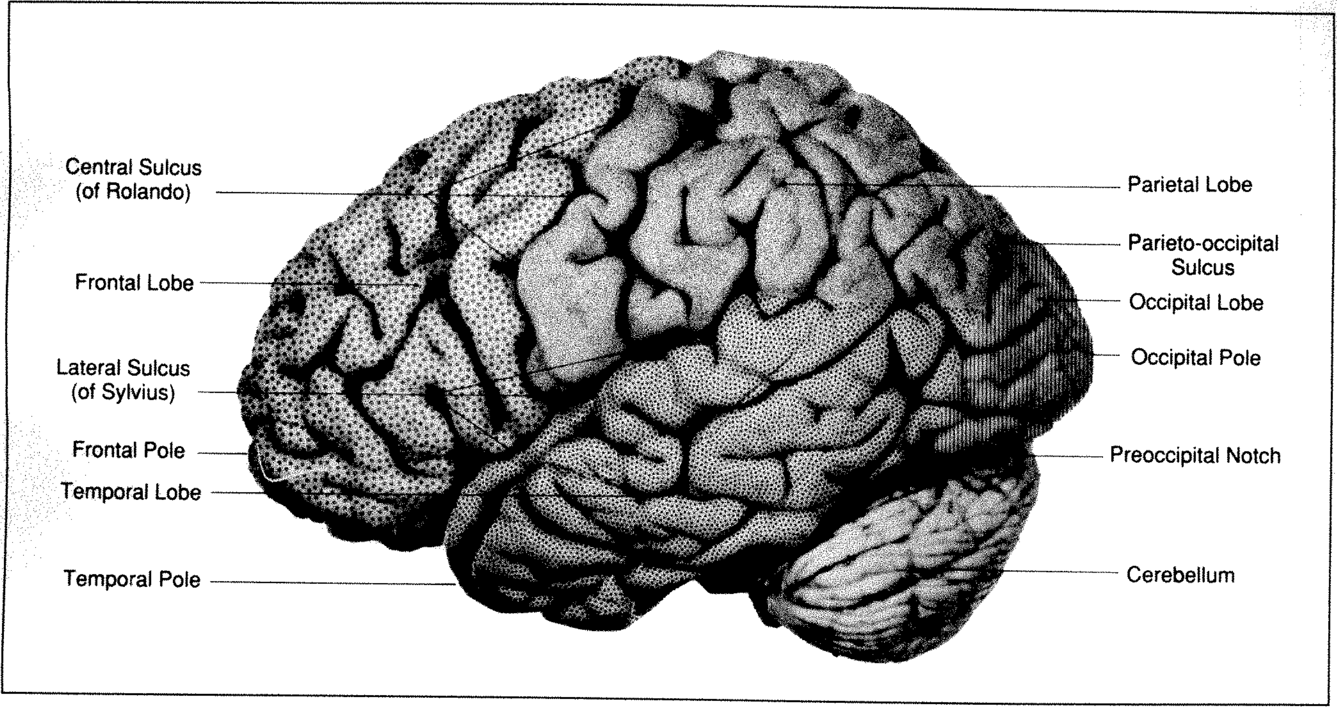

Fig 2.—The lateral surface of the brain (from Montemurro and Bruni[23]). The primary lobes of the cortex are designated by stippling. Gross structural features such as the fissure of Rolando and the sylvian fissure provide partial lobar boundaries on the cortical surface. However, no gross anatomical landmarks are present on the surface of the posterotemporal and inferoparietal lobes to define their boundary, and a somewhat arbitrary line is drawn. The anterior border of the occipital lobe also lacks surface landmarks for precise localization.

bottom of the cerebellar hemispheres and extending through the vertex.

Further manipulations to derive the measures for this study were then made by trained operators, who were "blind" to subject age or group status, using a stylus-controlled cursor on the displayed "pixel-classified" images.

Definition of Subcortical Structures

To delineate subcortical structures, the operators circumscribed pixels classified as gray matter that were visually determined to be in caudate nuclei, lenticular nuclei, and diencephalic gray-matter structures (including mammillary bodies, hypothalamic gray matter, septal nuclei, and thalamus). They did not trace the edges of the structures but defined polygons that included all gray-matter pixels within the structures, and excluded those gray-matter pixels associated with other structures. In some cases, when the subcortical nuclei were contiguous with other areas classified as gray matter but clearly not in the structures, boundaries were manually constructed.

Definition of Cerebral Regions

To define anatomically consistent cerebral regions, a method was adopted for making subdivisions of the cerebrum relative to the centromedial structural midline and two consistently identifiable points: the most anterior midline point in the genu and the most posterior midline point in the splenium of the corpus callosum. By calculating rotation angles using these landmarks, a three-dimensional rotation of the images was performed, thus correcting each individual's image data for rotation out of the optimal imaging plane. Regions could then be constructed that resulted in highly consistent placement of regional boundaries relative to gross anatomical landmarks.

The orientation of the midsagittal plane was first determined by computing a regression line through a series of visually selected brain-stem midline points. The division of the cerebrum was then based on two major planes (Fig 3): an axial plane, which is perpendicular in orientation to the midsagittal plane and parallel to the plane passing through the two corpus callosum points, and a coronal plane, which is defined as perpendicular to the first plane and which passes through the midpoint between the two corpus callosum points. The placement of the axial plane was standardized to the maximum z axis extent of the cerebrum, at 64% of the distance from the bottom of the cerebrum. This distance was chosen because it consistently reached the top of the highest of the two sylvian fissures in a group of eight subjects.

By computing new coordinates for each voxel relative to these planes, each is assigned to one of four zones: one, inferior to the axial plane and anterior to the coronal plane (IA); two, inferior to the axial plane and posterior to the coronal plane (IP); three, superior to the axial plane and anterior to the coronal plane (SA); and four, superior to the axial plane and posterior to the coronal plane (SP). Again, these defined planes are independent of the image plane, as a three-dimensional rotation is first applied based on the positions of the landmarks described earlier. This division resulted in the inclusion of all posterior perisylvian cortical structures in the IP zone; however, the occipital lobe was also included in this zone. Similarly, the IA zone included anterotemporal and frontal cortical structures.

To separate occipital from temporoparietal areas in the IP zone, and prefrontal from anterotemporal areas in the IA zone, two additional coronal dividing planes were defined. In the IA zone, a plane was defined that was parallel to the central plane and passed through the midline genu point. Similarly, in the IP zone, a plane was defined that was parallel to the central plane and that was positioned along the centromedial midline at a distance that consistently fell near the parieto-occipital sulcus. Thus, the two inferior zones were subdivided into four zones, described in gross terms as follows: the first (IA1), the most anterior, included prefrontal cortex; the second (IA2) included anterotemporal and anterior insular cortex; the third (IP1) included posterotemporal, posterior insular, and perisylvian parietal cortex; and the fourth (IP2), the most posterior, included mostly occipital and some posterotemporal cortex on the lateral surface. Figures 3 and 4 illustrate the location of the six cerebral zones defined by these planes. The division of brain structures into the zones is summarized in Table 2.

The regional boundaries are defined relative to the corpus callosum landmarks and the midsagittal plane. Therefore, they do not represent precisely defined neuroanatomical regions. Nevertheless, remarkable consistency in the placement of the boundaries, relative to all recognizable gross features, was observed. Regional maps, such as that seen in Fig 4, were generated for each subject in the study, and each was inspected to

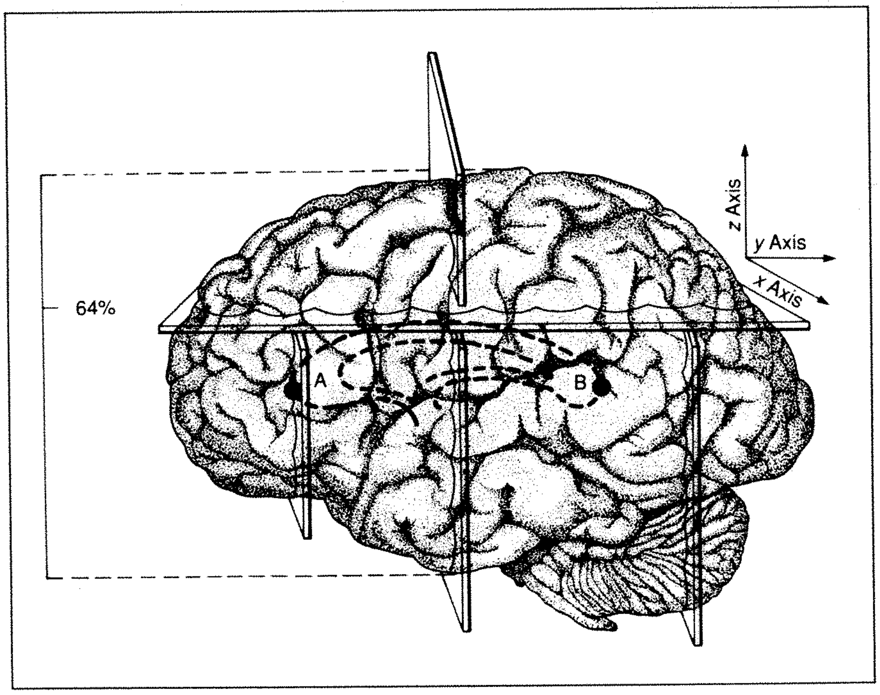

Fig 3.—Cerebral regions are defined as follows. Points A and B in the corpus callosum are the most anterior midline point in the genu and the most posterior midline point in the splenium, respectively. An axial plane, parallel to the plane passing through these two points, is defined as shown, perpendicular to the midsagittal plane. This plane is placed 64% of the distance from the bottom to the top of the supratentorial cranial vault. A coronal plane is defined perpendicular to the axial plane and passing through the midpoint between points A and B. Within the region below the axial dividing plane, two further (parallel) coronal dividing planes are defined, one passing through the genu midline point and one passing through the parieto-occipital sulcus. Thus, six cerebral zones are defined: inferoanterior 1, inferoanterior 2, inferoposterior 1, inferoposterior 2, superoanterior, and superoposterior.

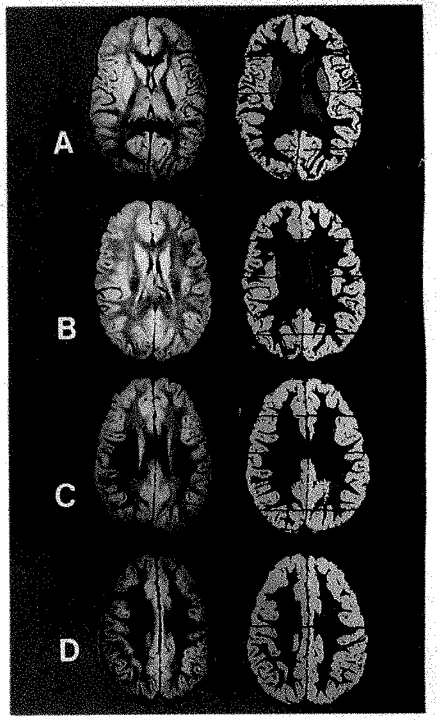

Fig 4.—Representative, fully processed images displayed adjacent to the original proton density–weighted images. Pixels are classified, and zones have been manually designated. The gray-matter pixels have been color coded to display the structural designations: right hemisphere cortical is yellow; left hemisphere cortical, white; caudate, blue; lenticular nucleus, pink; and diencephalon, green. Hyperintense areas within the subcortical regions are shown in gray. Cerebrospinal fluid and white-matter pixels in all regions are displayed in red and black, respectively; however, these pixels are coded so that regional measures may be computed. Sections in A through C are entirely inferior to the axial dividing plane. The section in D is completely superior to the dividing plane. For inferior and superior zones, the central line indicates the position of the major coronal dividing plane. In the inferior zone, two additional lines indicate the positions of the two secondary coronal dividing planes.

ensure that the regions did not vary discernibly in terms of the structures included. In all cases, the inferior zone extended to the highest point in the sylvian fissure that could be recognized in the images. From inspection of the images, Table 2 was compiled to assist in the interpretation of the results. It is not meant to convey the impression that precise boundaries were defined between the structures mentioned.

The total number of supratentorial voxels (including CSF, hyperintensities, and gray and white matter) was computed, by hemisphere, for each of the six zones. Cerebral asymmetry of each of the zones was expressed as a ratio of the left hemisphere measure to its right hemisphere counterpart. Thus, when the left region was larger than the right, the ratio was greater than 1. Volumes of the subcortical gray-matter structures were estimated by summing the appropriate voxels in each hemisphere. All volume estimates are given as simple totals of designated voxels. As described above, each voxel is 4.39 mm^3. However, an estimate of true volume should probably treat the 5-mm sections as representative of the 7.5-mm interslice distance; thus, each voxel would represent 6.49 mm^3. Areas within the lenticular nucleus containing significant iron deposits, particularly in the globus pallidus, do not meet the signal criteria for gray matter and are thus excluded from this region.

A comparison of the original proton density–weighted images and the fully processed images is illustrated in Fig 4. In this figure, the different pixel classes are color coded as follows: right hemisphere cortical gray matter is yellow; left hemisphere cortical gray matter, white; diencephalic areas, green; caudate nuclei, blue; lenticular nuclei, pink; and fluid and white matter, red and black, respectively. Pixels in the subcortical region shown in gray are areas within white matter or surrounding the ventricles that have higher T_2 values than other white matter regions. The blue lines running through the sections indicate the positions of the coronal dividing planes. For this set of images, the boundary between the inferior and superior zones fell between sections C and D.

Statistical Analyses

Group means for the measures were compared with Student's *t* tests. The comparisons of the six asymmetry measures test the hypothesis that cerebral development is anomalous in the L/LI children. Because of multiple asymmetry comparisons, $P<.01$ was required to reject the null hypothesis. The other comparisons are provided for descriptive purposes only. The meaning of statistical significance of individual test statistics in the context of multiple tests is ambiguous, and probabilities are provided for the secondary comparisons only to aid in interpretation of patterns. Inferences about structural abnormalities from these post hoc comparisons must be made with caution.

RESULTS

On routine clinical neuroradiological evaluation, 16 of 20 examinations in the L/LI children were unremarkable. Slight asymmetry of the ventricles (right larger) was noted in one male subject. One boy and one girl had tiny foci of hyperintensity in deep white matter. In one male participant, bilateral areas of encephalomalacia were present just lateral to the caudate nuclei, with the larger right lesion measuring 8 mm in width.

Among the control children, eight of 12 examinations were unremarkable. Tiny foci of hyperintensity were noted in one boy and one girl. A right cerebellar venous angioma was noted in one boy. A small pituitary gland was noted

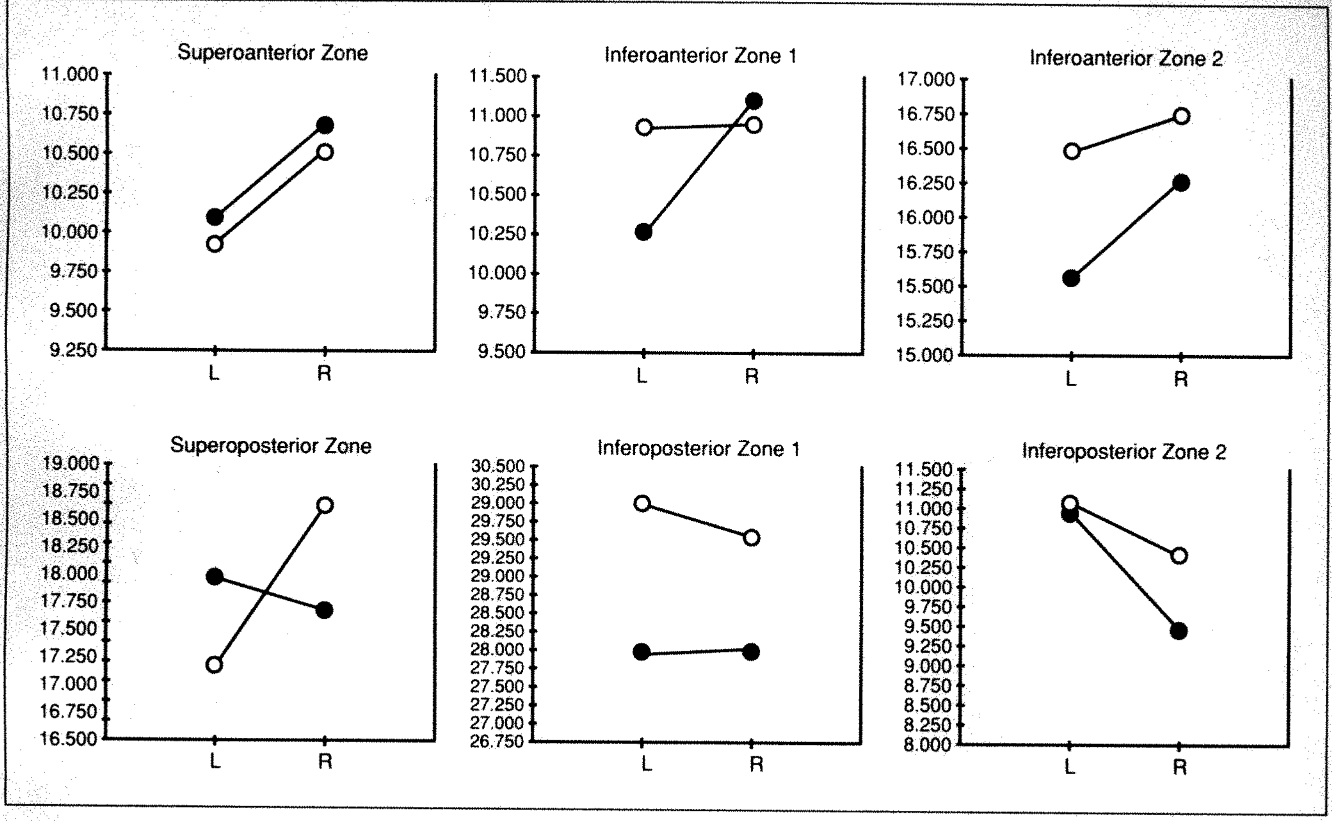

Fig 5.—Mean estimated volumes in thousands of voxels are plotted for each hemisphere by cerebral region. Open circles denote control values; closed circles, values from learning- and language-impaired subjects. All subjects, including left-handers, are included.

Table 2.—Summary of Cortical Structures Within Each Cerebral Region

- **Inferoanterior 1**
  - Prefrontal cortex inferior to plane above frontal operculum, including orbitofrontal, dorsolateral, and mesial frontal lobe
- Inferoanterior 2 (IA2)
  - Temporal poles, uncus, and some amygdala; anterior perforated substance and adjacent orbitofrontal cortex; anterior insular cortex and frontal operculum
- Inferoposterior 1
  - Most of temporal lobe, including all mesial temporal lobe structures posterior to amygdala (only temporal pole is included in IA2); perisylvian parietal cortex and parietal operculum
- Inferoposterior 2
  - Most of occipital lobe (only small portion of superior occipital cortex is included in SP); small part of most posterior gyri of temporal lobe on lateral cortical surface
- Superoanterior
  - Superior parts of dorsolateral and mesial frontal lobes (above frontal operculum)
- Superoposterior (SP)
  - Superoparietal lobe above parietal operculum; small portion of most superior occipital lobe

Table 3.—Group Differences on Cerebral Asymmetries*

Region	Ratios (L/R) Controls	Ratios (L/R) L/LI	*t*	*P*
IA1	1.00 ± 0.04 (1.00 ± 0.04)	0.92 ± 0.07 (0.93 ± 0.06)	3.68 (3.12)	.001 (.004)
IA2	0.99 ± 0.04 (0.98 ± 0.04)	0.96 ± 0.05 (0.97 ± 0.04)	1.66 (1.10)	.107 (.280)
IP1	1.02 ± 0.03 (1.01 ± 0.03)	1.00 ± 0.05 (1.01 ± 0.04)	0.97 (0.30)	.339 (.764)
IP2	1.06 ± 0.10 (1.06 ± 0.10)	1.17 ± 0.16 (1.17 ± 0.16)	2.12 (2.15)	.043 (.041)
SA	0.95 ± 0.10 (0.96 ± 0.09)	0.95 ± 0.07 (0.94 ± 0.06)	0.11 (0.68)	.913 (.503)
SP	0.93 ± 0.07 (0.93 ± 0.08)	1.02 ± 0.08 (1.01 ± 0.07)	3.17 (2.79)	.003 (.010)

*Values are mean ± SD. Results omitting left-handed subjects are given in parentheses. L/LI indicates language and learning impaired; IA1 and IA2, inferoanterior 1 and 2; IP1 and IP2, inferoposterior 1 and 2; SA, superoanterior; and SP, superoposterior.

in another boy. Thus, incidental findings on routine clinical evaluation of the images did not reveal consistent parenchymal or structural differences between the groups.

Group comparisons of cerebral asymmetries in the six regions are summarized in Table 3. The pattern observed only in right-handed subjects is the same as that observed in the full sample. Both IA1 and SP asymmetries are significantly different in the L/LI group ($P<.01$ in each case). The ratio is significantly decreased in the IA1 region and significantly increased in the SP region. An illustration of the different patterns of asymmetry (for the full sample) is provided in Fig 5, showing group mean volumes for the right and left hemispheres within each region. In the normal controls, the IA1 regions are symmetrical, while in the L/LI children, the left hemisphere is reduced relative to the right. For the SP region, the normal controls show right-larger asymmetry, while an opposite pattern is observed in the L/LI subjects.

Secondary analyses focused on the hemispheric volumes of the cerebral (cranial) regions and the subcortical nu-

Table 4.—Group Differences in Cerebral Volumes*

	Volume, Voxels			
	Controls	L/LI	t	P
Cerebral regions				
L IA1	11 125 (11 286)	10 373 (10 277)	1.52 (1.96)	.14 (.06)
R IA1	11 137 (11 361)	11 303 (11 135)	0.27 (0.36)	.79 (.72)
L IA2	16 456 (16 695)	15 539 (15 492)	1.46 (1.86)	.16 (.07)
R IA2	16 693 (16 977)	16 236 (16 069)	0.64 (1.24)	.53 (.23)
L IP1	29 990 (30 163)	27 990 (27 743)	2.18 (2.55)	.04 (.02)
R IP1	29 545 (29 793)	28 032 (27 517)	1.69 (2.77)	.10 (.01)
L IP2	11 027 (10 919)	10 907 (10 559)	0.20 (0.62)	.85 (.54)
R IP2	10 375 (10 343)	9455 (9121)	1.66 (2.37)	.11 (.03)
L SA	9943 (10 073)	10 117 (9976)	0.31 (0.17)	.76 (.87)
R SA	10 527 (10 553)	10 698 (10 693)	0.27 (0.20)	.79 (.84)
L SP	17 231 (17 333)	18 004 (17 615)	1.05 (0.45)	.30 (.66)
R SP	18 650 (18 664)	17 708 (17 549)	1.33 (1.46)	.19 (.16)
Subcortical structures				
L caudate	1031 (1034)	966 (945)	1.61 (2.35)	.12 (.03)
R caudate	1046 (1042)	971 (954)	1.75 (2.08)	.09 (.05)
L lenticular	1257 (1242)	1178 (1171)	1.32 (1.18)	.20 (.25)
R lenticular	1196 (1182)	1126 (1117)	1.19 (1.09)	.24 (.29)
L diencephalic gray	1427 (1411)	1358 (1342)	1.30 (1.28)	.20 (.21)
R diencephalic gray	1439 (1426)	1319 (1301)	2.21 (2.21)	.04 (.04)

*Results omitting left-handed subjects are given in parentheses. Abbreviations are as in Table 3.

Table 5.—Asymmetries in Posterior Perisylvian Region*

	Hemisphere Symmetry (L:R Ratio)		
	R > L (≤0.99)	Symmetrical (0.99-1.01)	L > R (≥1.01)
Controls	1 (1)	4 (4)	7 (6)
L/LI	10 (8)	1 (1)	9 (9)

*Results omitting left-handed subjects are given in parentheses. L/LI indicates language and learning impaired. For total group, Pearson $\chi^2 = 7.9$, $df = 2$, $P = .019$; for group omitting left-handed subjects, Pearson $\chi^2 = 6.5$, $df = 2$, $P = .038$.

clei. Table 4 summarizes group comparisons of these measures. Although many mean volumes are lower in the L/LI group, when examining the full sample, of the cerebral region measures, that in the left IP1 region (posterior perisylvian) is particularly reduced in the L/LI group. Among the subcortical structures, only the right diencephalic volume is notably reduced, although the right caudate measure is also low. The exclusion of left-handers resulted in somewhat larger group differences on these measures, so that left and right IP1 regions appear to be reduced, as is right IP2, and the caudate reductions are slightly more prominent. Though they are not presented herein, no left-right asymmetry in the subcortical volumes yielded a group difference with $P<.05$. Also, because cortical gray-matter volumes were available for right and left hemisphere of each of the six regions, regional cortical asymmetry measures were computed. The pattern of group differences was the same as that for the cranial regions, with significant differences in regions IA1 and SP.

Because earlier studies have classified subjects categorically based on their posterior asymmetries, we examined our data for evidence that the mean asymmetries may have obscured differences in distribution. Indeed, the variance for the asymmetry measures in region IP1 was significantly larger in the L/LI sample than in the control sample ($P<.05$). Therefore, a post hoc frequencies analysis was performed. Table 5 gives the asymmetries in categorical form. The L/LI group did have a somewhat higher prevalence of reversed asymmetries. A χ^2 statistic suggested that the distributions were indeed different; however, the small frequencies in some cells render the statistical test suspect.

Measures of ventricular and sulcal size, as well as proportions of gray to white matter, were similar in the two groups, as assessed with quantitative methods. Furthermore, there was no evidence for abnormal signal values in the white matter in the L/LI children as a group. In summary, there was no evidence from the group comparisons for significant damage to or loss of tissue in the form of increased CSF or hyperintense white matter areas.

COMMENT

The pattern observed in the control subjects of this study suggests that within hemispheres roughly equal in size overall, significant regional asymmetries do occur, with posterior structures larger on the left in inferior and larger on the right in superior zones. In frontal areas, the volumes are symmetrical in the inferior zone, and the right hemisphere volume is larger in the superior zone. The posterior asymmetries seem to be consistent with left hemisphere specialization for language in the posterior temporal lobes and right hemisphere specialization for spatial functions in the parietal lobes. Furthermore, these asymmetries, as well as the frontal asymmetry in the superior zone, are consistent with earlier reports of regional asymmetries in normal subjects.[14-21]

Regarding the absolute values obtained on the asymmetry measures, a caveat should be entered about possible spatial distortion due to field inhomogeneity.[22] Thus, although these results suggest that in both groups the hemispheres are nearly the same size, ie, the left-right ratio has a mean of 0.99 in controls and 1.00 in L/LI children, one or both of the hemispheres may have been systematically measured inaccurately owing to magnification or minification in some parts of the magnetic field. Nevertheless, such factors should have affected both groups similarly.

The L/LI children in this study were selected at 4 years of age because of specific developmental delays in language function in the context of preserved sensory, motor, and nonverbal intellectual capacities. After 5 years of study, at 9 years of age, they have continuing significant, in some cases severe, language and learning impairment. Gross brain structure was remarkably normal in this group of children. There was little evidence for parenchymal damage or volume loss, except in one case. There is definite evidence, however, for anomalous brain development in the form of altered cerebral shape. The L/LI children show abnormal asymmetry, but it does not appear in the posterior perisylvian regions, where it was expected. Rather, these children show an aberrant (right greater than left) asymmetry in the prefrontal region, and an aberrant (left greater than right) asymmetry in the parietal region. Closer inspection of the posterior perisylvian measures, however, reveals a possible explanation for this surprising result. There is evidence from the secondary analyses that this region of the left hemisphere is reduced in volume. Even when this regional volume is expressed as a percentage of the overall supratentorial volume (sum of the regions), it still shows evidence of a proportional decrease in the L/LI children relative to the controls ($P<.05$). However, inspection of the comparable right hemisphere volume also suggests reduction. Thus, the asymmetry is only slightly affected in this region by the (probably bilateral) volume reduction.

Some earlier imaging studies of developmental language disorders[7,8] have produced evidence of an increased prevalence of reversed asymmetry in posterior hemispheric regions. Such studies generally group the subjects in terms of the direction of their asymmetries. To address these findings directly, we conducted post hoc analyses of the distribution of our posterior perisylvian asymmetries. There was weak statistical evidence that more of the L/LI children showed reversed asymmetry (right greater than left). It, therefore, seems prudent to point out that our results should not be interpreted as refuting the earlier findings and, indeed, they provide some supportive evidence for the presence of more frequent reversals in this region.

The question arises whether the findings in these children are similar to neuropathological results in dyslexic children,[4,5] and whether the anomalous asymmetries in this study could have occurred as a result of the mechanisms hypothesized to account for dyslexia.[6] The planum temporale was not specifically examined in this study, owing to the difficulty of reliably determining its boundaries. Thus, the results do not bear directly on the pathological study results. This structure did always fall within the much larger posterior perisylvian region (IP1), where, although the L/LI children showed more variable asymmetries, no significant mean asymmetry difference was found. The pattern observed in this region might appear to be inconsistent with the reported increase in the size of the right planum in dyslexia. The structures in IP1, including the planum but many others as well, are reduced in volume on the left and are nearly as reduced on the right, relative to controls. Similarly, examination of the pattern within the prefrontal region (IA1), where the L/LI children show greater (right greater than left) asymmetry, suggests that the aberration is more likely to be due to reduction of left structures than to preservation of right structures. In the parietal (SP) region, where the L/LI group shows a reversal of the normal (right greater than left) asymmetry, the right hemisphere is smaller in volume in the L/LI group, while the left is larger, although neither difference is itself statistically significant.

Galaburda and colleagues[4-6] found no evidence for a reduction in neuronal populations in the brains of their dyslexic subjects. Rather, they found evidence for disordered migration and possibly enhanced survival of neurons in critical nondominant hemisphere structures. The subjects examined herein may not be representative of the same population. Although many of them are dyslexic, they were not chosen for isolated reading disorders. Longitudinal study of these children suggests more pervasive linguistic and academic limitations, and evidence indicates that in some children overall intellectual abilities have lagged further and further behind peer standards with increasing age. It is possible that the subjects examined herein suffered effects on neurodevelopment at an earlier stage of neurogenesis, leading to reduced cell populations in critical perisylvian structures (hence, the early prominence of their language disturbances) and ultimately to altered cerebral shape. Interestingly, reduced neuronal populations in left hemisphere insular cortex were noted in one neuropathological study of developmental dysphasia.[3] Even if this explanation is correct, it is still unclear whether the shape alterations observed herein are entirely due to decreased volume of certain affected structures, or if they evolve as early alterations, or exert later effects on mechanisms of cortical maturation and specialization such as those proposed by Galaburda.[6] It is even possible that neuronal loss in related structures may have led to altered maturation of the plana in the subjects of the present study, such that enlarged right plana are present within perisylvian regions that are themselves reduced in volume overall. Perhaps further neuropathological studies in a broader range of developmental disorders may shed some light on these questions.

This study confirms that anomalous neurodevelopment in this disorder does produce structural aberration at a level measurable with in vivo brain imaging. The correlation of such measurements with specific behavioral indices, as development proceeds, may provide some insight into the brain mechanisms involved in developmental cognitive disorders.

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References

1. Benton AL. Developmental aphasia and brain damage. *Cortex*. 1964;1:40-52.

2. Landau WM, Goldstein R, Kleffner FR. Congenital aphasia: a clinicopathological study. *Neurology*. 1960;10:915-921.

3. Cohen M, Campbell R, Yaghmai F. Neuropathological abnormalities in developmental dysphasia. *Ann Neurol*. 1989;25:567-570.

4. Galaburda AM, Kemper TL. Cytoarchitectonic abnormalities in developmental dyslexia: a case study. *Ann Neurol*. 1979;6:94-100.

5. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive patients with cortical anomalies. *Ann Neurol*. 1985;18:222-233.

6. Galaburda AM. The pathogenesis of childhood dyslexia. *Res Publ Assoc Res Nerv Ment Dis*. 1988;66:127-137.

7. Hier DB, LeMay M, Rosenberger PB, Perlo VP. Developmental dyslexia. *Arch Neurol*. 1978;35:90-92.

8. Rosenberger PB, Hier DB. Cerebral asymmetry and verbal intellectual deficits. *Ann Neurol*. 1980;8:300-304.

9. Haslam RHA, Dalby JT, Johns RD, Rademaker AW. Cerebral asymmetry in developmental dyslexia. *Arch Neurol*. 1981;38:679-682.

10. Rumsey JM, Dorwart R, Vermess M, Denckla MB, Kruesi MJP, Rapoport JL. Magnetic resonance imaging of brain anatomy in severe developmental dyslexia. *Arch Neurol*. 1986;43:1045-1046.

11. Hynd GW, Semrud-Clikeman M. Dyslexia and brain morphology. *Psychol Bull*. 1989;106:447-482.

12. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders*, *Third Edition*. Washington, DC: American Psychiatric Association. 1980.

13. Jernigan TL, Press GA, Hesselink JR. Methods for measuring brain morphologic features on magnetic resonance images: validation and normal aging. *Arch Neurol*. 1990;47:27-32.

14. Witelson SF, Pallie W. Left hemisphere specialization for language in the newborn. *Brain*. 1973;96:641-646.

15. Wada JA, Clarke R, Hamm A. Cerebral hemispheric asymmetry in humans. *Arch Neurol*. 1975;32:239-246.

16. Chi JG, Dooling EC, Gilles FH. Left-right asymmetries of the temporal speech areas of the human fetus. *Arch Neurol*. 1977;34:346-348.

17. LeMay M. Morphological cerebral asymmetries of modern man, fossil man, and nonhuman primate. *Ann N Y Acad Sci*. 1976;280:349-366.

18. LeMay M, Kido DK. Asymmetries of the cerebral hemispheres on computed tomograms. *J Comput Assist Tomogr*. 1978;2:471-476.

19. Chui HC, Damasio AR. Human cerebral asymmetries evaluated by computed tomography. *J Neurol Neurosurg Psychiatry*. 1980;43:873-878.

20. Geschwind N, Galaburda AM. Cerebral lateralization: biological mechanisms, associations, and pathology, I: a hypothesis and a program for research. *Arch Neurol*. 1985;42:428-459.

21. Bear D, Schiff D, Saver J, Greenberg M, Freeman R. Quantitative analysis of cerebral asymmetries: fronto-occipital correlation, sexual dimorphism, and association with handedness. *Arch Neurol*. 1986;43:598-603.

22. Jack CR, Gehring DG, Sharbrough FW, et al. Temporal lobe volume measurement from MR images: accuracy and left-right asymmetry in normal persons. *J Comput Assist Tomogr*. 1988;12:21-29.

23. Montemurro G, Bruni J. *The Human Brain in Dissection*. 2nd ed. New York, NY: Oxford University Press Inc; 1988:38.

Allochiria vs *Allesthesia*

Is There a Misperception?

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• Allochiria is the mislocation of sensory stimuli to the corresponding opposite half of the body or space. Obersteiner (1882) introduced the term *allochiria* (Greek *allos* = other + *chiria* = hand), and more than 20 authors employed it in this context over the next 25 years. Stewart (1894) described a related phenomenon in which stimuli are displaced to a different point on the same extremity. He noted that the displacements were different than allochiria and coined the term *allachaesthesia* (ie, *allesthesia*) (Greek *allaché* = elsewhere + *aisthésis* = perception). Despite this historical background, Jones (1907) redefined both terms in an attempt to increase diagnostic specificity and attributed allochiria to hysteria. Jones' reinterpretation does not appear to be justified historically, etymologically, or scientifically and has resulted in contradictory definitions of *allochiria* and *allesthesia* in present-day medical dictionaries and neurologic textbooks. We advocate a return to usage consistent with the original descriptions and word derivations.

(*Arch Neurol.* 1991;48:546-549)

The purpose of our article is to delineate the origins and historical development of the terms *allochiria* and *allesthesia*. The account is of interest not only from a historical perspective, but also because of the present confusion in terminology. For example, a review of seven current medical dictionaries[1-7] reveals numerous inconsistencies. First, a variety of orthographic representations are available. Allochiria is listed as *allochiria* (the original) or *allocheiria*. Allesthesia is listed as *allachaesthesia* (the original), *allesthesia, allachesthesia, allaesthesia, allochaesthesia, allochesthesia,* or *alloesthesia*. Second, and more important, a variety of denotations are offered that are inconsistent across, and even within, texts (Table 1). Ignoring the various orthographic differences, allochiria and allesthesia are given different definitions in two dictionaries, only allochiria is listed in one dictionary, and four dictionaries list allochiria and allesthesia as synonymous terms, although one of these dictionaries does give a different definition to one orthographic form of allesthesia (ie, *allachesthesia*), even though the same Greek roots are listed. Textbooks of neurology[8-11] exhibit no better consistency (Table 2). Such diversity does not reflect specific scientific terminology. How is it then that we have come to such a state of confusion?

In 1882, the famous Austrian neuropathologist and neuroanatomist Heinrich Obersteiner founded the Neurologische Institut at the University of Vienna. In that same year, he published an article in *Brain*,[12] in which he introduced the term *allochiria* from the Greek roots *ἄλλοζ* (other) and *χείρ* (hand) to denote a "confusion of sides" seen in patients during tactile stimulation. Obersteiner stated,[12]

> This symptom is so easy to determine that no long description is required. When we test the sensibility of a patient, on the leg for example, and find that the two points of the aesthesiometer are recognized as such at a moderate distance apart, or when a prick or pressure is fairly localised, and yet, as frequently occurs, the irritation is referred to the other side, we have the condition before us. The power of localisation is retained as to details, while doubt or error exists as to the side touched, the irritation being commonly referred to the corresponding part of the other limb. I believe that the phenomenon is less rare than overlooked, as errors on the part of the patient are apt to be regarded as merely a *lapsus verbi*. In the case of intelligent patients, however, and with due care, it soon becomes apparent that this is not the true explanation.

Obersteiner described four cases in detail, including three patients with myelopathy (one traumatic and two tabetic) and one case of presumed hysteria.[12] In addition, he reviewed six cases of tabes from the literature reported by Fischer (1880), Hertzberg (1875), and Von Leyden (1863) in which similar symptomatology had been described but only attributed to a generalized disorder of sensory localization. In contrast, Obersteiner noted,[12]

> Allochiria may be manifested when the power of localisation has only suffered to a slight degree, so that, with the exception of the error as to the side, the place touched was quite correctly indicated. It would therefore be erroneous to look upon allochiria merely as a symptom of great sensory impairment. I am of opinion it must be regarded as a completely distinct symptom

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by itself. In favour of this also may be adduced the fact that, in very many cases of central neurosis, allochiria is altogether absent, notwithstanding the presence of a marked degree of anaesthesia.

Although uncertain as to the underlying mechanisms, Obersteiner suggested that the allochiria in the cases of myelopathy might be related to degeneration of the posterior columns. From a physiological perspective, he felt that his observations showed "that there is an intimate connection, in a sensory relationship, between corresponding regions of the body."[12]

Six months later, David Ferrier[13] reported another case of allochiria in *Brain* (1883), confirming "Obersteiner's view that allochiria must be regarded as a symptom not necessarily associated with anaesthesia." The patient had been under Ferrier's care at King's College Hospital, London, England, in 1881-1882. While engaged in his work as a carpenter, the patient had suffered a severe cranial injury when a scaffold-pole fell on his head from "some considerable height."[13] The major sequelae included ataxia and left hemiparesis. In regard to the sensory findings, Ferrier reported,[13]

> Tactile sensibility is throughout normal as regards delicacy and quickness of response, but there is a most remarkable condition of allochiria, or localisation of impressions on the wrong side, as well as a similar reversal of reflex response to tactile stimuli. . . . A touch on the right big toe was at once referred to the same spot on the left, and *vice versâ;* a similar condition existing on every point of both legs up to the groin. Above this, impressions were exactly localized on their proper side. . . . But, as has been stated, the reversal was not confined to perception of impressions, but extended also to reflex reaction. Tickling the sole of the one foot caused retraction of the other, while the foot actually tickled remained perfectly still. So also tickling of the inside of the one thigh caused flexion of the other. Conjoint tickling of the sole of the one foot and the inside of the other thigh caused reflex reactions of the foot and thigh.
>
> The unhesitating precision with which the patient referred the impression to the corresponding point on the side not touched, led me at first to suspect deception; but the absolute uniformity of the phenomena under every precaution against the patient knowing what was being done to test the condition, together with the reversal also of the reflex reactions, compelled me to abandon this hypothesis.

In the 25 years following Obersteiner's original description, 76 cases were reported to which the term allochiria was applied.[14] The majority were related to the sense of touch, but allochiric responses were also noted in relationship to pain, "muscle sense,"

Table 1.—Medical Dictionary Definitions of *Allochiria* and *Allesthesia*

Dictionary	Term	Greek Root	Definition
Black's Medical Dictionary[1]	*Allesthesia*	. . .	Not listed
	Allocheiria	. . .	Disorder of sensation in which sensations are referred to the wrong part of the body
Butterworths Medical Dictionary[2]	*Allachaesthesia* Allaesthesia	allache = elsewhere + aesthesia = no definition given	Touch sensation referred to a place distant from the point at which stimulus has been applied, but on the same side of the body; cf *allocheiria*
	Optical allachaesthesia	. . .	Transfer of an image by illusion from its proper quadrant in the visual field to the quadrant in a diagonal line opposite
	Allochaesthesia	. . .	Allachaesthesia
	Allocheiria	allos = other + cheir = hand	Alloaesthesia
Dorland's Illustrated Medical Dictionary[3]	*Allesthesia*	allos = other + aisthesis = perception-ia	A condition in which a sensation, as of pain or touch, is experienced at a point remote from that at which the stimulus is applied or occurs, as in allochiria
	Visual allesthesia	. . .	A condition in which visual images are transposed from one half of the visual field to the other, either vertically or horizontally; called also optical allachesthesia
	Allochiria	allo + cheir = hand + -ia	A condition in which, if one extremity is stimulated, the sensation is referred to the opposite side (Obersteiner)
Gould Medical Dictionary[4]	*Allachesthesia,* allachaesthesia	allache = elsewhere + esthesia	A tactile sensation experienced remote from the point of stimulation but on the same side of the body
	Allaesthesia	. . .	Allachesthesia
	Allesthesia, allaesthesia	. . .	Allachesthesia
	Allochaesthesia	. . .	Allachesthesia
	Allocheiria	allo + cheir- + ia	A form of allachesthesia in which the tactile sensation is experienced on the side opposite; the one to which the stimulus was applied, seen in tabes dorsalis and other conditions
	Allochesthesia, allochaesthesia		Allachesthesia
International Dictionary of Medicine and Biology[5]	*Allocheiria*	allo- + cheir- + -ia	Alloesthesia
	Allochesthesia	. . .	Alloesthesia
	Allochiria	allo(s) = other + cheir = hand + -ia	Alloesthesia
	Alloesthesia	allo- + -esthesia	A disorder of the localization of tactile stimuli, in which the patient feels the sensation at a corresponding point on the opposite side of the body to that to which the stimulus is applied. Also called allocheiria, allochiria, allochesthesia, Bamberger sign

(Continued on p 548.)

Table 1.—Medical Dictionary Definitions of *Allochiria* and *Allesthesia* (cont)

Stedman's Medical Dictionary[6]	*Allesthesia*	allos = other + aisthesis = sensation	Allocheira: alloesthesia; Bamberger's sign (2); a form of allachesthesia in which the sensation of a stimulus in one limb is referred to the opposite limb
	Visual allesthesia	. . .	A disorder characterized by the transposition of images from one half-field to the opposite
	Allocheiria, allochiria	allo- + cheir = hand	Allesthesia
	Allochiria	. . .	Alternative spelling for allocheiria (allesthesia)
Taber's Cyclopedic Medical Dictionary[7]	*Allesthesia*	allos = other + aisthesia = sensation	Perception of stimulus in the opposite limb from the one stimulated. Syn: allochesthesia; allochiria
	Allochesthesia	allache = elsewhere + aisthesia = sensation	Allesthesia
	Allochiria, allocheiria	allos = other + cheir = hand	Allesthesia

Table 2.—*Allochiria* and *Allesthesia* in Selected Neurology Textbooks

Clinical Neurology[8]	Optic allesthesia (false orientation of objects in space)
	Visual allesthesia is the transposition of an image to the opposite half of the field of vision
	A tactile stimulus applied to one part of the body may be projected to a corresponding spot on the opposite side (tactile allochiria)
	Pain induced by normally innocuous stimuli due to hyperesthesia of the region is known as allochiria
	The sudden appearance of pain in the homologous area of the body following cordotomy was due to reference pain also called allochiria
Medical Neurology[9]	Allochiria is a confusion of sides (ie, left from right) . . . This is a form of agnosia seen in lesions in or near the dominant angular gyrus as part of the Gerstmann syndrome
Principles of Neurology[10]	In alloesthesia or allesthesia, a tactile or painful stimulus delivered on the side of hemisensory loss is experienced in a corresponding area of the opposite side; this abnormality is observed most frequently with right-sided putaminal lesions (usually hemorrhage) and with anterolateral lesions of the cervical spinal cord
	Patients with an attention hemianopia may displace an image to the nonaffected half of the field of vision (visual allesthesia)
	False orientation of objects in space (optic allesthesia)
The Neurologic Examination[11]	The terms allachesthesia, allesthesia, and synesthesia are used when the sensation of touch is experienced at a site remote from the point of stimulation; allochiria means the referring of a sensation to the opposite side of the body

temperature, vision, smell, taste, hearing, and even reflex electrical movements. Allochiria was described as occurring in a number of diverse pathologic conditions, but most frequently in conjunction with tabes dorsalis or hysteria.[14] In their textbook, *Diseases of the Nervous System* (1899), Gowers and Taylor[14] defined allochiria as "a condition in which an impression on one part has been referred to the corresponding place on the opposite side of the body. Similar definitions were also employed by Ferrier, Church, Féré, Gay, Bury, Osler, F. Taylor, Head, Spearman, Hammond, Stewart, Marie, Dejerine, Brown-Séquard, Longuet, Gellé, Lapidous, Henri, Nothnagel, Strumpell, Von Leyden, Huber, Weiss, Hoffman, and Morselli.[14]

T. Grainger Stewart, who was later to collaborate with Gordon Holmes on important studies of cerebellar pathology, introduced the term *allachaesthesia* (ie, *allesthesia*) in an article published in the *British Medical Journal* in 1894.[15] Stewart described a 49-year-old man with a variety of somatic complaints and physical findings. The most striking neurological findings included a "perverted localization of sensation" in the left hemibody, rhythmical jerking of the right leg, chorea-like movements of the left leg and right hand, and an odd three-step corkscrew gait.[15] The major point of Stewart's article related to the sensory findings. In both the left arm and leg, he observed consistent horizontal displacements of localization for touch from the medial to the lateral portions, and vice versa. On the left trunk, horizontal and diagonal displacements were present. Stewart felt "that this and all our patient's symptoms are functional."[15] He noted the resemblance of these displacements to allochiria, but stated that they were obviously not the same since the displacements were on the same side of the body. In concluding, he designated a new name for this type of displacement[15]:

> The name allochiria has proved so useful in relation to the symptom which Obersteiner described, that I have thought it well to try to coin an expression which may serve as a name for this kind of faulty localisation, and, after consulting with my colleague, Professor Butcher, have decided to suggest the name, "allachaesthesia," from α'λλαχῆ, or α'λλαχοῦ, elsewhere, and α'ισθησία, perception, as the most satisfactory term that occurs to us.

Despite this precedence, Ernest Jones decided to redefine allochiria and allesthesia in an attempt to enhance the diagnostic specificity of allochiria.[14] Jones was a colleague and friend of Sigmund Freud. Jones aided Freud in his escape from Austria when the Nazis took power and was one of Freud's few colleagues who stayed with him to the end. After Freud's death, Jones authored a massive three-volume biography of his friend. Needless to say, Jones had an interest in hysteria. In 1907, he published one article in *Brain*[14] and one article in *Lancet*[16] reviewing the literature and detailing his view that allochiria "is always of psychical origin and that its presence is almost certain evidence of hysteria."[16]

To support his contention, Jones quoted Obersteiner out of context stating that allochiria is a condition in which "sensibility is retained more or less completely."[14] In fact, Obersteiner had pointed out that allochiria could occur with other sensory impairments, but could not be explained solely by simple sensory loss. Jones separated "true" allochiria from "false" allochiria (ie, allesthesia), and stated,[14]

> Obersteiner, who like all subsequent writers, did not recognise the distinction between the two classes, gave instances of both conditions in the cases he described in his original article. The one condition, false allochiria, is nothing more or less than alloaesthesia.... the mistake in alloaesthesia is essentially due to incomplete perception of the stimulus and is accompanied by many other failures in perception, such as defective localisation.

By redefining the terminology, Jones felt justified in claiming that allochiria had a "precise diagnostic value" and that the occurrence of allochiria "should be regarded as a positive indication of the presence of hysteria."[14] But, was he justified either historically or scientifically? Historically, his definitions do not fit the word derivations, the intent of the original authors, or even the general usage by the scientific community of that era. Scientifically, we know that allochiria, even under the restricted terms given by Jones, is not limited to hysteria. For example, cases that Jones would have attributed to a simple general sensory defect in localization (allesthesia by his definition) cannot be explained in this manner since the stimulus displacements are to the exact corresponding points on the opposite body. Further, a simple sensory defect cannot explain palinoptic visual allesthesia (ie, a persistent visual image in a spatial location remote from original stimulus).

Jones asserted that "it would be very curious if a peculiar phenomenon like allochiria could be produced in two quite different ways."[14] In fact, it would be more curious if such a complex behavioral symptom that spans such a variety of underlying disease processes (eg, myelopathies, neglect syndrome, diffuse organic brain syndromes, hysteria, and parieto-occipital tumors with palinoptic visual allochiria) could be explained by a single mechanism. Jones confused symptom with function, a mistake commonly made in the 19th century regarding localization of function, and a mistake that continues in this century despite the writings of Hughlings Jackson and others. Like most neurologic signs and symptoms, allochiria takes on its anatomic and pathophysiologic significance from the full pattern of neurologic findings. For example, the allochiria seen in myelopathies may depend on an uncrossed ipsilateral spinothalamic pathway,[10] but allochiria following right-sided cerebral lesions may depend on alterations in attentional/intentional mechanisms.[17]

The views expressed by Jones in his articles of 1907 were not seriously challenged, and, excluding studies on local sensory displacements (eg, Henry Head), writings on allochiria and allesthesia all but disappeared until the middle of the 20th century, when Morris Bender[18] began his extensive studies on the phenomenon of sensory displacement. In 1948, Bender described a case of transbody tactile mislocations in a patient exhibiting "slight impairment of two point discrimination and point localization." He employed the term *allesthesia*, accepting Jones' definition that "allochiria" can occur only in the complete absence of sensory deficits.[19] However, simple sensory deficits cannot explain the transbody mislocations, a point that is all the more clear in later cases described by Bender and colleagues.[20] For example, a graphic depiction of mislocations in a patient with left-sided hypalgesia from a 1949 article by Bender et al[20] demonstrates dramatically that the mislocations do not occur in a random pattern, which would be expected if produced by a simple defect in localization. The use of *allesthesia* in these cases is not strictly incorrect since allochiria is a subset of allesthesia. However, the use of *allochiria* is more precise since it implies a different phenomenon that cannot be explained by a simple sensory deficit.

In conclusion, Jones' reinterpretation of allochiria and allesthesia is not justified historically, etymologically, or scientifically, and has resulted in contradictory definitions in present-day medical dictionaries and neurological textbooks.[1-11] We advocate a return to usage more consistent with the original descriptions and word derivations. Thus, *allesthesia* is a condition in which a sensory impression is mislocated to a remote position, and *allochiria* denotes mislocations to the corresponding opposite half of the body or space.

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References

1. Havard CWH. *Black's Medical Dictionary.* Totowa, NJ: Barnes & Noble Books; 1987.
2. Critchley M. *Butterworths Medical Dictionary.* London, England: Butterworths; 1978.
3. Friel JP. *Dorland's Illustrated Medical Dictionary.* Philadelphia, Pa: WB Saunders Co; 1981.
4. Osol A. *Blakiston's Gould Medical Dictionary.* New York, NY: McGraw-Hill International Book Co; 1972.
5. Landau SI. *International Dictionary of Medicine and Biology.* New York, NY: John Wiley & Sons Inc; 1986.
6. Stedman TL. *Stedman's Medical Dictionary.* Baltimore, Md: Williams & Wilkins; 1976.
7. Thomas CL. *Taber's Cyclopedic Medical Dictionary.* Philadelphia, Pa: FA Davis Co; 1981.
8. Joynt RJ, ed. *Clinical Neurology.* Revised ed. Philadelphia, Pa: JB Lippincott Co; 1989.
9. Gilroy J, Meyer JS. *Medical Neurology.* 2nd ed. New York, NY: Macmillan Publishing Co Inc; 1975.
10. Adams RD, Victor M. *Principles of Neurology.* 4th ed. New York, NY: McGraw-Hill International Book Co; 1989.
11. DeJong RN. *The Neurologic Examination.* 4th ed. New York, NY: Harper & Row Publishers Inc; 1979.
12. Obersteiner H. On allochiria. *Brain.* 1882; 4:153-163.
13. Ferrier D. Case of allochiria. *Brain.* 1883; 5:389-393.
14. Jones E. The precise diagnostic value of allochiria. *Brain.* 1907;30:490-532.
15. Stewart TG. A clinical lecture on a case of perverted localisation of sensation or allachaesthesia. *BMJ.* 1894;1:1-4.
16. Jones E. The clinical significance of allochiria. *Lancet.* 1907;5:830-832.
17. Meador KJ, Loring DW, Lee GP, et al. Right cerebral specialization for tactile attention as evidenced by intracarotid sodium amytal. *Neurology.* 1988;38:1763-1766.
18. Bender MB. *Disorders of Perception.* Springfield, Ill: Charles C Thomas Publishers; 1952.
19. Bender MB, Wortis SB, Cramer J. Organic mental syndrome with phenomena of extinction and allesthesia. *Arch Neurol Psychiatry.* 1948; 59:273-291.
20. Bender MB, Shapiro MF, Teuber HL. Allesthesia and disturbance of body scheme. *Arch Neurol Psychiatry.* 1949;62:222-235.

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Observation

Germ Cell Tumors Masquerading as Central Nervous System Sarcoidosis

David M. Peeples, MD; Barney J. Stern, MD; Violet Jiji, MD; K. Singh Sahni, MD

• The diagnosis of central nervous system sarcoidosis is uncertain without typical multisystem involvement. We describe two patients with isolated central nervous system mass lesions whose biopsy results were consistent with sarcoidosis. After a progressive clinical course, they were found to have diencephalic germinomas. Germ cell tumors, in particular, should be considered in the differential diagnosis of central nervous system sarcoidosis as they are potentially treatable, occur in intracranial locations favored by sarcoidosis mass lesions, and may be surrounded by granulomatous inflammation that can be mistaken for the noncaseating granulomas of sarcoidosis.

(*Arch Neurol.* 1991;48:554-556)

Intracranial granulomatous mass lesions can arise from diverse pathogenic mechanisms. Infectious processes, inflammatory disorders, and neoplastic disease can all result in granulomatous reactions. Sarcoidosis can present with isolated central nervous system (CNS) involvement,[1] occasionally in the form of a mass lesion[2]; systemic manifestations are typically found or develop over time. We describe two patients with diencephalic granulomatous mass lesions that were initially thought to represent CNS sarcoidosis, but were found, after relentless progression, to be germ cell tumors.

REPORT OF CASES

CASE 1.—A 37-year-old white man presented in October 1985 with polyuria and polydipsia. Evaluation revealed a partial antidiuretic hormone deficiency, positive purified protein derivative tuberculin, and a 2.5-cm suprasellar contrast-enhancing mass on computed tomographic scan. A chest roentgenogram revealed old granulomas. Results of lacrimal gland biopsy and angiotensin-converting enzyme levels were normal, as were serum and cerebrospinal fluid β–human chorionic gonadotrophin and α-fetoprotein levels. A stereotactic biopsy specimen showed a mononuclear cell infiltrate consistent with granulomatous disease. The patient was treated with desmopressin acetate (dDAVP), isoniazid, and rifampin. In October 1986, diminished visual acuity occurred, and computed tomographic scans revealed a slight increase in the size of the lesion (Fig 1, left). The diagnosis of sarcoidosis was made, and prednisone therapy (80 mg/d) was initiated. In December 1986, the patient developed headaches, a postchiasmatic syndrome with a right homonymous hemianopsia and a left inferior quadrantanopsia, and tinnitus and hearing loss in the right ear. His cerebrospinal fluid was acellular (protein, 0.96 g/L; and glucose, 3.2 mmol/L). He underwent surgical exploration in January 1987; the mass had a friable appearance and was adherent to the hypothalamus. Pathologic examination revealed inflammatory cells with a granulomatous reaction consistent with sarcoidosis. Acid-fast bacilli and fungal stains and cultures were negative. Prednisone therapy (140 mg/d) improved the patient's visual and aural symptoms, but by April 1987 he again developed progressive visual loss and constricted visual fields. Complete reevaluation for systemic sarcoidosis was negative, and in May 1987 cyclosporine was administered in addition to prednisone as part of an investigational study for refractory neurosarcoidosis. In July 1987 the findings of the patient's neurologic examination were unchanged, but a computed tomographic scan of his cranium revealed further enlargement of the mass (Fig 1, right). He developed *Pneumocystis carinii* pneumonia and died after a respiratory arrest.

Autopsy revealed a 5.5 × 2.0 × 1.1-cm pedunculated mass composed of gray, somewhat rubbery tissue protruding from the sella turcica, involving both optic nerves, the optic chiasm, and the pituitary stalk, and loosely adherent to the base of the third ventricle and hypothalamus. Microscopic examination revealed a germinoma composed of sheets of large round cells with pale cytoplasm and hyperchromatic nuclei. Lymphoid cells were infiltrating between the tumor cells and fibrovascular stroma. No granulomas were seen (Fig 2). The eighth cranial nerves were normal.

CASE 2.—A 16-year-old white boy presented in January 1987 with headaches, papilledema, and a small enhancing lesion obstructing the foramen of Monroe (Fig 3, left). Ventriculoperitoneal shunting was followed by a right frontal craniotomy and a biopsy, which revealed a granulomatous reaction in the floor of the third and left lateral ventricles, consistent with sarcoidosis (Fig 4, left). There was no tumor found, and acid-fast bacilli, fungal, and mucin stains were negative. Analysis of cerebrospinal fluid showed 8

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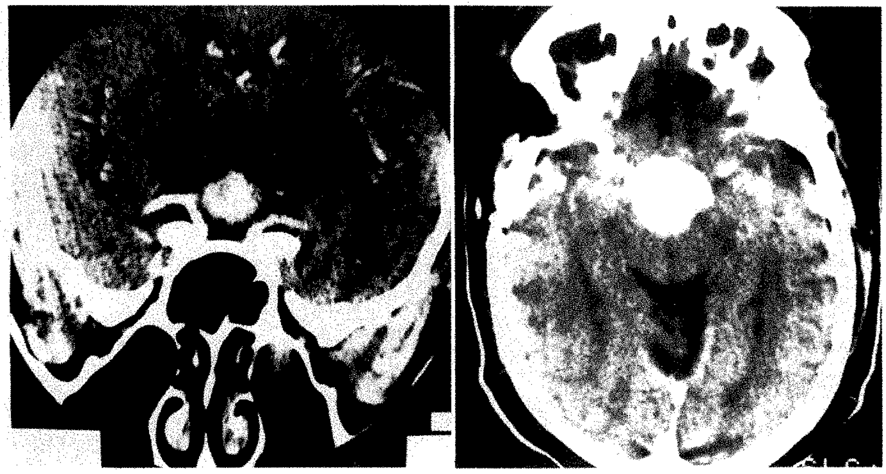

Fig 1.—Left, Contrast-enhanced computed tomographic scan of patient 1 reveals a discrete suprasellar mass. Right, Contrast-enhanced computed tomographic scan of the same patient 9 months later shows enlargement of the mass.

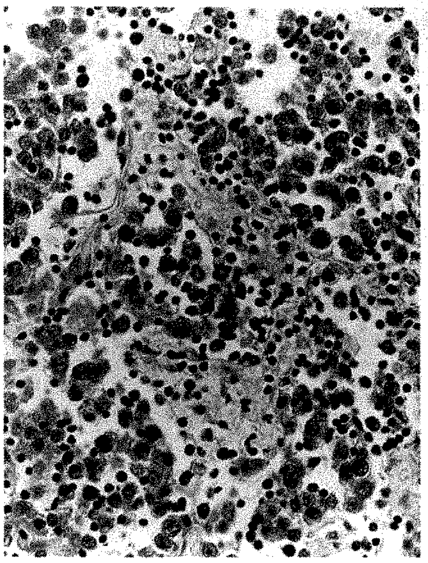

Fig 2.—Representative histologic section of the germinoma obtained at autopsy of patient 1 reveals characteristic germinoma cells in a loose vascular stroma with interspersed lymphocytes (hematoxylin-eosin, ×320).

monocytes; protein, 0.34 g/L; and glucose, 4.3 mmol/L; the cytopathologic findings were negative. Systemic evaluation for sarcoidosis was unrevealing. Prednisone therapy (40 mg/d) was initiated. In July 1987 a computed tomographic scan revealed extensive enhancement in the anterior third ventricle and hypothalamus. The patient developed mild central hypopituitarism, with slightly low thyrotropin, thyroxine, and testosterone levels. Weekly infusions of methylprednisolone (30 mg/kg) were begun, but by September 1987 there was a 3-cm intraventricular enhancing mass (Fig 3, right), and a hypothalamic syndrome with hyperpyrexia, hypersomnolence, and diabetes insipidus had developed. In October 1987 a large heterogeneous third ventricular mass was removed. Pathologic examination revealed malignant germinoma, composed predominantly of embryonal carcinoma and focal teratoma (Fig 4, right). There was extensive necrosis and granulomatous inflammation. An immunoperoxidase α-fetoprotein stain was positive. Postoperatively, the patient did poorly, with rapid tumor recurrence despite radiation therapy and chemotherapy. He died of sepsis several months later.

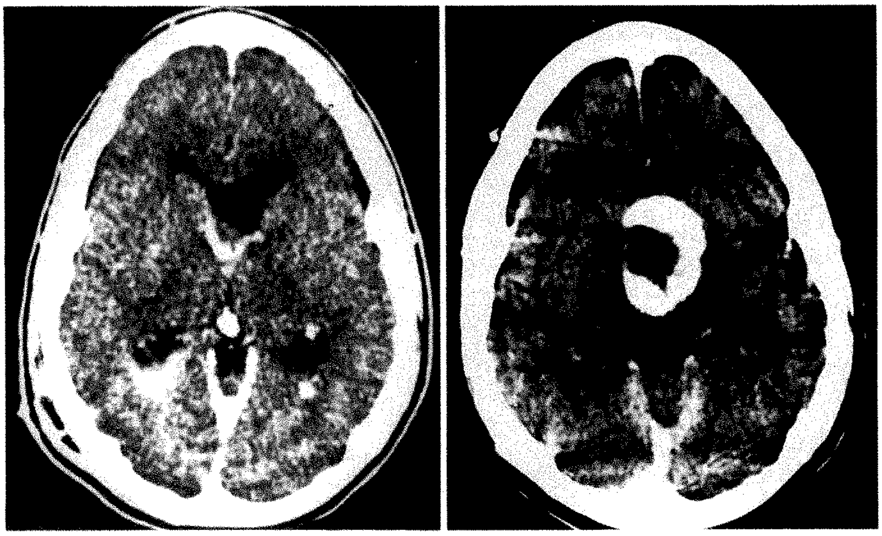

Fig 3.—Left, Contrast-enhanced computed tomographic scan of patient 2 reveals an enhancing lesion near the third ventricle and dilatation of the left lateral ventricle. Right, Contrast-enhanced computed tomographic scan of the same patient 8 months later reveals a large cystic mass.

COMMENT

Sarcoidosis is a multisystem granulomatous disease of unknown origin with neurologic manifestations in 5% of cases.[1,3,4] Nearly 50% of patients with neurosarcoidosis will have neurologic symptoms as the initial feature of their illness. Although rare, isolated granulomatous mass lesions can be the sole clinical manifestation of sarcoidosis.[2] The suprasellar region is a characteristic site, and diabetes insipidus, as in our first patient, is not an unusual presentation.[5] Nevertheless, multisystem involvement is the rule: one autopsy study found disseminated disease to be common despite isolated neurologic symptoms,[6] and another clinical series of 50 consecutive patients with neurosarcoidosis reported that of 24 who presented with neurologic symptoms, systemic involvement eventually developed in all but five.[1]

Both our patients were white males who lacked the stigmata of multisystem sarcoidosis such as elevated serum angiotensin-converting enzyme levels, adenopathy, uveitis, or pulmonary inflammation. Neurosarcoidosis was entertained on the basis of biopsy of the CNS lesion, twice in our first patient, which revealed no evidence of neoplasia or infection. Although a granulomatous CNS mass lesion could be either true isolated CNS sarcoidosis or simply a harbinger of systemic involvement, the lack of evidence for multisystem sarcoidosis makes a diagnosis, even on the basis of biopsy, far less certain. Furthermore, concurrent corticosteroid treatment can make detection of inflammation in other organs difficult.

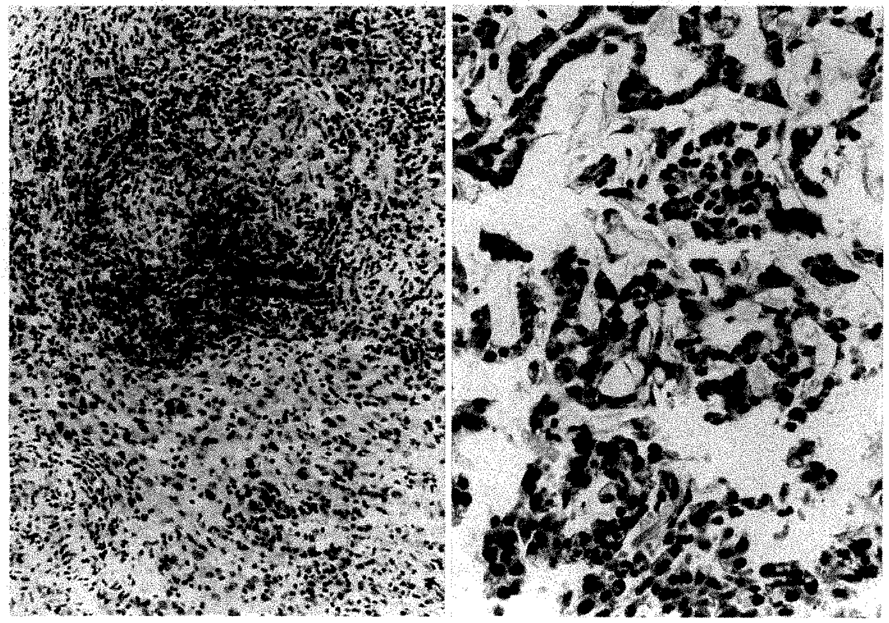

Fig 4.—Left, Section of open biopsy specimen from patient 2 reveals granulomatous inflammation (hematoxylin-eosin, ×320). Right, Second biopsy specimen obtained 8 months later shows a malignant germ cell tumor with features of an embryonal carcinoma (hematoxylin-eosin, ×320).

Although noncaseating granulomas are the pathologic hallmark of sarcoidosis, granulomatous inflammation is nonspecific and must be considered within the clinical framework. Granuloma formation can arise from diverse processes including tuberculosis, atypical mycobacteria, fungal infections, syphilis, brucellosis, actinomycosis, tularemia, leprosy, vasculitis, and foreign body reactions and as a response to certain neoplasms. Histologically, the sarcoidosis granuloma is composed of large pale-pink epithelial cells with interspersed giant cells and lymphocytes. Caseation is not prominent, but may occur and cause confusion with tuberculosis. Schaumann's and asteroid bodies are perhaps most common in sarcoidosis granulomas, but they are not pathognomonic features and cannot be reliably used as diagnostic criteria.[7]

The treatment of CNS sarcoidosis mass lesions typically begins with corticosteroid therapy. In refractory cases, or when decompensation is imminent owing to mass effect, high-dose corticosteroid therapy, treatment with other immunosuppressive agents, surgical exploration, and radiotherapy are often considered.[4] These interventions can occasionally lead to further diagnostic confusion. For instance, lymphoma may respond to corticosteroid or radiation therapy. The possibility of alternative diagnoses should always be kept in mind and aggressively excluded.

Intracranial germ cell tumors, also called atypical teratoma or ectopic pinealoma, are rare.[8] They usually occur in the pineal region, causing increased intracranial pressure and Parinaud's ophthalmoplegia. A suprasellar location is the second most common site. Diabetes insipidus can be an early sign, with the late development of hypopituitarism, hypothalamic dysfunction, visual field defects, and raised intracranial pressure. Symptoms and sites of involvement are strikingly similar to sarcoidosis mass lesions. Furthermore, a granulomatous reaction is common in the periphery of such lesions, and the malignancy can be missed on biopsy if the core of the tumor is not obtained.[9] Some germinomas secrete α-fetoprotein, β–human chorionic gonadotrophin, or placental alkaline phosphatase.[10] An elevated cerebrospinal fluid angiotensin-converting enzyme level has been documented in a patient with a suprasellar germinoma,[11] a finding that can occur in CNS sarcoidosis and thereby further contribute to diagnostic confusion.[12] One of our patients had no tumor markers at presentation, and the other was not evaluated prior to tumor debulking, at which time the tissue had a positive α-fetoprotein immunoperoxidase stain. It is possible that if elevated cerebrospinal fluid levels of α-fetoprotein had been detected, an earlier diagnosis might have been possible. There is an excellent response of germ cell tumors to radiotherapy,[8,13,14] highlighting the importance of accurate diagnosis.

Without the stigmata of multisystem disease, basing the diagnosis of CNS sarcoidosis on the biopsy specimen of a mass lesion demonstrating noncaseating granulomas is fraught with uncertainty. Our two cases illustrate several important aspects in the management of patients with granulomatous mass lesions from presumed isolated CNS sarcoidosis: (1) The diagnosis of CNS sarcoidosis is most certain if multisystem disease is demonstrated. (2) Biopsy of a mass lesion can miss the primary pathologic process and reveal only a nonspecific granulomatous reaction. (3) If clinical progression occurs, with enlargement of the mass lesion despite aggressive corticosteroid therapy, continued search for systemic disease and another biopsy, if possible, are indicated to rule out infection or neoplasia. (4) Corticosteroid therapy may mask the stigmata of disease at other sites. (5) Germ cell tumors, in particular, need to be considered because they are potentially treatable, frequently occur at intracranial locations favored by sarcoidosis, and have a prominent surrounding granulomatous reaction.

Richard J. Otenasek, Jr, MD, referred patient 2. We thank Ed Koo, MD, who reviewed the pathology specimens, and Gwendolyn Boyd and Charlie Harper, who helped prepare the manuscript.

References

1. Oksanen V. Neurosarcoidosis: clinical presentations and course in 50 patients. *Acta Neurol Scand.* 1986;73:283-290.
2. Norwood CW, Kelly DL. Intracerebral sarcoidosis acting as a mass lesion. *Surg Neurol.* 1974;2:367-372.
3. Delaney P. Neurologic manifestations in sarcoidosis: review of the literature with a report of 23 cases. *Ann Intern Med.* 1977;87:336-345.
4. Stern BJ, Krumholz A, Johns CJ. Neurosarcoidosis: presentation and management. *Ann N Y Acad Sci.* 1986;465:722-730.
5. Pennell WH. Boeck's sarcoid with involvement of the central nervous system. *Arch Neurol Psychiatry.* 1951;66:728-737.
6. Gailloud C, Rabinowicz T. Sarcoidose et systeme neuveux central. *Doc Ophthalmol.* 1969;25:248-281.
7. Robbins SL, Cotran RS. Infectious diseases. In: *Pathologic Basis of Disease.* Philadelphia, Pa: WB Saunders Co; 1979:477-478.
8. Takeuchi J, Handa H, Nagata I. Suprasellar germinoma. *J Neurosurg.* 1978;49:41-48.
9. Kaspar C, Schneider N, Childers J, Wilson J. Suprasellar germinoma: unresolved problems in diagnosis, pathogenesis, and management. *Am J Med.* 1983;75:705-711.
10. Javadpour N. The role of biologic tumor markers in testicular carcinoma. *Cancer.* 1980; 45:1755-1761.
11. Rohmer V, Saint-Andre JP, Alhenc-Gelar F, Corvol P, Bigorgne J. Angiotensin I converting enzyme in a suprasellar germinoma. *Am J Clin Pathol.* 1987;87:281-284.
12. Oksanen V, Fyhrquist F, Somer H, Gronhagen-Riska C. Angiotensin converting enzyme in cerebrospinal fluid: a new assay. *Neurology.* 1985;35:1220-1223.
13. Fields J, Fulling K, Thomas P, Marks J. Suprasellar germinoma: radiation therapy. *Radiology.* 1987;164:247-249.
14. Sung D, Harisiadis L, Chang C. Midline pineal tumors and suprasellar germinoma: highly curable by irradiation. *Radiology.* 1978;128:745-751.

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WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft ip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have eceived phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all nterrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to pileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent r correct this defect and has been recommended to be given to the mother before delivery and o the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs f toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack f induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug scontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-ohnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be sumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has ompletely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin edication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced henytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar g, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same atients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been ported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to henytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. ppropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and sence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversib dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recomm reduction of phenytoin therapy is indicated if plasma levels are excessive; if symp termination is recommended. (See Warnings.)

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2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic al reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains c which interfere with the absorption of phenytoin. Ingestion times of phenytoin preparations containing calcium should be staggered in patients with low serum phe to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: ph sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarb acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitat susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired b include: corticosteroids, coumarin anti digitoxin, doxycycline, estrogens, furos contraceptives, quinidine, rifampin, th vitamin D.

Drug/Laboratory Test Interactions: Phe cause decreased serum levels of protein-b (PBI). It may also produce lower than norm dexamethasone or metyrapone tests. Phe cause increased serum levels of glucose, al phatase, and gamma glutamyl transpepti

Carcinogenesis: See "Warnings" section f tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this dr phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations with phenytoin therapy are referable to this system and are usually dose-related. Th nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. insomnia, transient nervousness, motor twitchings, and headaches have also been obse have also been rare reports of phenytoin induced dyskinesias, including chorea, dysto and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patient long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver

Integumentary System: Dermatological manifestations sometimes accompanied b included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) i common; other types of dermatitis are seen more rarely. Other more serious forms be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosu Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally bee in association with administration of phenytoin. These have included thrombocytope penia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone m pression. While macrocytosis and megaloblastic anemia have occurred, these conditi respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperpl dolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warning

Connective Tissue System: Coarsening of the facial features, enlargement of the lip hyperplasia, hypertrichosis and Peyronie's Disease.

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OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Othe tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient ma comatose and hypotensive. Death is due to respiratory and circulatory depression.

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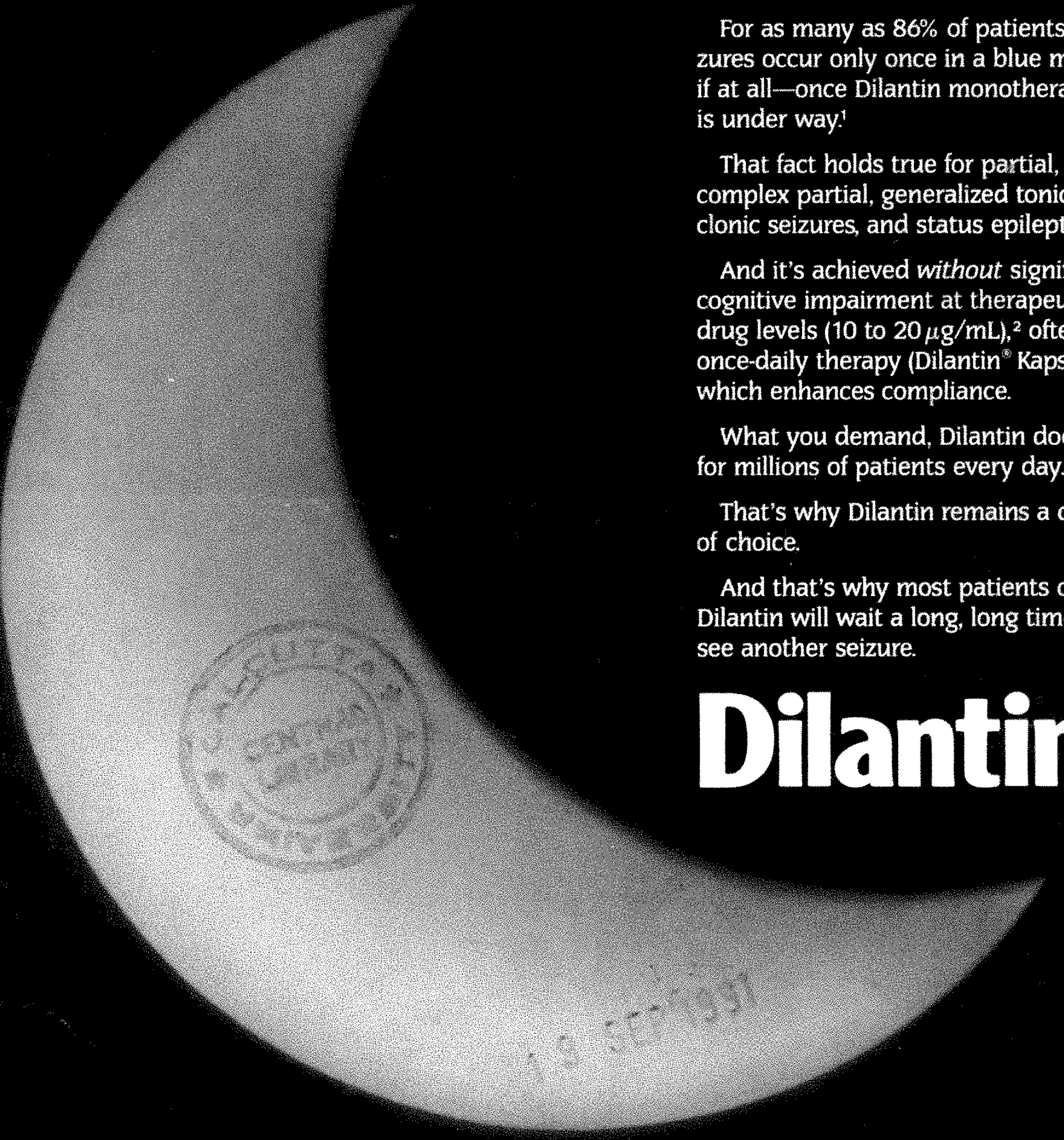

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"Once in a blue moon" describes the phenomenon in which the moon appears as a brilliant blue. Seen worldwide following the volcanic eruption of Krakatoa in 1883, the blue moon occurs only when atmospheric cloud droplets, each less than 5 μm in diameter, form in abundance—an exceedingly rare event.[3]

References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976; 31:292-296

Please see adjacent page for brief summary of prescribing information.

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12/11/92

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ARCHIVES OF Neurology

JUNE 1991

A Comparison of Daily and Alternate-Day Prednisone Therapy in the Treatment of Duchenne Muscular Dystrophy

G. M. Fenichel, J. R. Mendell, R. T. Moxley III, R. C. Griggs, M. H. Brooke, J. P. Miller, A. Pestronk, J. Robison, W. King, L. Signore, S. Pandya, J. Florence, J. Schierbecker, B. Wilson

---

Vegetative State After Closed-Head Injury: A Traumatic Coma Data Bank Report

H. S. Levin, C. Saydjari, H. M. Eisenberg, M. Foulkes, L. F. Marshall, R. M. Ruff, J. A. Jane, A. Marmarou

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The Influence of Gender on the Susceptibility to Multiple Sclerosis in Sibships

A. D. Sadovnick, D. E. Bulman, L. Hashimoto, M. B. D'Hooghe, G. C. Ebers

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Incidence and Prevalence of Amyotrophic Lateral Sclerosis in Harris County, Texas, 1985-1988

J. F. Annegers, S. Appel, J. R.-J. Lee, P. Perkins

Estimated Prevalence of Dementia Among Elderly Black and White Community Residents

A. Heyman, G. Fillenbaum, B. Prosnitz, K. Raiford, B. Burchett, C. Clark

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Volume 48, Number 6

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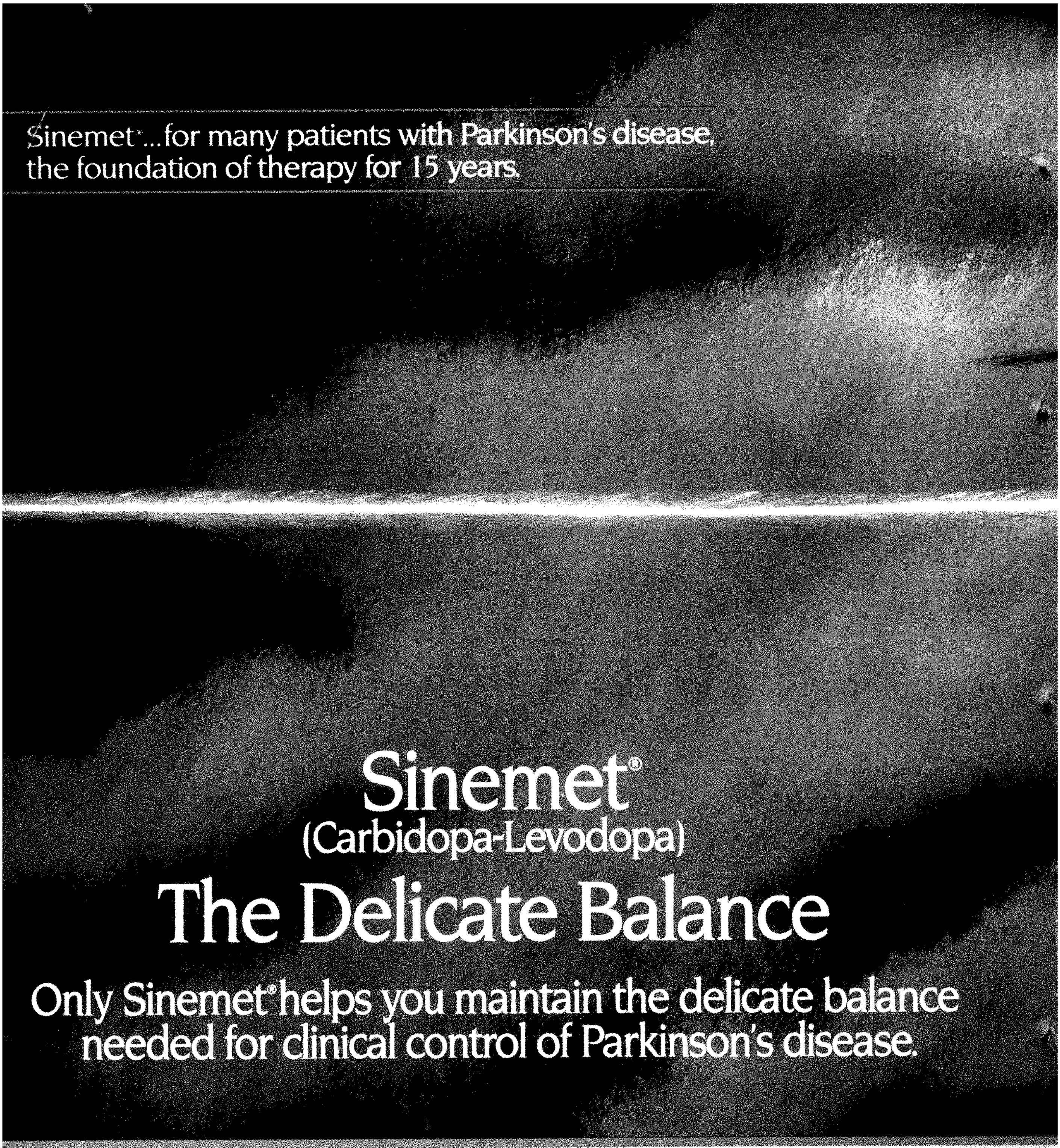

Sinemet®...for many patients with Parkinson's disease, the foundation of therapy for 15 years.

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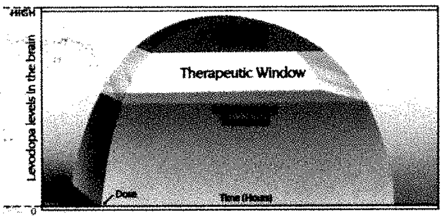
(Carbidopa-Levodopa)
The Delicate Balance

Only Sinemet® helps you maintain the delicate balance needed for clinical control of Parkinson's disease.



Balancing Dopamine Replacement and Patient Response *Managing the symptoms of Parkinson's disease can be an ongoing balancing act, particularly as the disease progresses and the therapeutic window changes. By adjusting Sinemet® dosage strength and frequency according to patient needs, physicians can achieve the delicate balance needed between dopamine replacement and therapeutic response.*

The management of levodopa therapy in Parkinson's disease can be complex. It calls for a delicate balance between the relief of symptoms by the replacement of dopamine in the brain and the occurrence of side effects.

Dopamine replacement is the mainstay of therapy in Parkinson's disease. Only Sinemet® re-establishes dopamine levels in the brain.

But, too much or too little dopamine can affect the patient's quality of life. So dosage must be monitored and adjusted as the disease progresses, because the therapeutic window narrows over time.

Sinemet® provides you the flexibility needed to adjust dosage based on the individual patient's therapeutic window...by changing dosing frequency...dosage strength... or by changing the ratio between carbidopa and levodopa.

Nothing else helps you maintain the delicate balance needed to manage the signs and symptoms of Parkinson's disease like Sinemet®.

Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower doses and sooner with Sinemet® than with levodopa. The occurrence of dyskinesias may require dosage reduction. Please see a brief summary of prescribing information on the adjoining page.

Sinemet®
(Carbidopa-Levodopa)

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For many patients with Parkinson's disease

Dosage Guidelines

Individualized dosage—a key to clinical success with Sinemet*

- Begin when symptoms first interfere with normal function
- Adjust as necessary to help maintain relief of symptoms

1

For initial therapy...Start with:

SINEMET 25-100

containing 25 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

one tablet t.i.d.

If necessary, to control symptoms, dosage may be increased by one tablet every day or every other day until a dosage of eight tablets of Sinemet 25-100 a day is reached.

2

When it is evident that patients need more levodopa...Transfer to:

SINEMET 25-250

containing 25 mg carbidopa (anhydrous equivalent) and 250 mg levodopa

one tablet t.i.d.

If still more levodopa is necessary, dosage with Sinemet 25-250 may be increased by one-half to one tablet every day or every other day to a maximum of eight tablets a day.

3

When individualizing dosage...Titrate with:

SINEMET 10-100

containing 10 mg carbidopa (anhydrous equivalent) and 100 mg levodopa

or SINEMET 25-100

or SINEMET 25-250

The optimum daily dosage of Sinemet must be determined by careful titration in each patient. Tablets of the three strengths may be given separately or combined as needed to provide the optimum daily dosage.

For patients transferred from levodopa

DISCONTINUE LEVODOPA AT LEAST 8 HOURS BEFORE STARTING SINEMET.

The starting dose for Sinemet should provide about 25 percent of previous levodopa requirements. (Patients receiving less than 1500 mg of levodopa a day should be started on one tablet of Sinemet 25-100 t.i.d. or q.i.d.)

Sinemet®
(Carbidopa-Levodopa)

When SINEMET is to be given to patients who are being treated with levodopa, levodopa must be discontinued at least 8 hours before therapy with SINEMET is started. In order to reduce adverse reactions, it is necessary to individualize therapy. See the WARNINGS (below) and DOSAGE AND ADMINISTRATION sections in the Prescribing Information before initiating therapy.

Contraindications: MAO inhibitors and SINEMET should not be given concomitantly. MAO inhibitors must be discontinued at least 2 weeks prior to initiating therapy with SINEMET.

SINEMET is contraindicated in patients with known hypersensitivity to this drug and in narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, it should not be used in patients with suspicious, undiagnosed skin lesions or history of melanoma.

Warnings: Levodopa must be discontinued at least 8 hours before SINEMET is started. SINEMET should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage. (See DOSAGE AND ADMINISTRATION section of Prescribing Information.) Patients taking SINEMET should be instructed not to take additional levodopa unless prescribed.

As with levodopa, SINEMET may cause involuntary movements and mental disturbances. These reactions may be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for development of depression with concomitant suicidal tendencies. Treat with caution patients with past or current psychoses. *Because carbidopa permits more levodopa to reach the brain and, thus, more dopamine to be formed, dyskinesias may occur at lower dosages and sooner with* SINEMET *than with levodopa.* Occurrence of dyskinesias may require dosage reduction.

SINEMET should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

Exercise care in administering SINEMET, as with levodopa, to patients with history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, there is possibility of upper GI hemorrhage in patients with history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

Usage in Pregnancy and Lactation: Although effects of SINEMET on human pregnancy and lactation are unknown, both levodopa and combinations of carbidopa and levodopa have caused visceral and skeletal malformations in rabbits. Use of SINEMET in women of childbearing potential requires that anticipated benefits of the drug be weighed against possible hazards to mother and child. SINEMET should not be given to nursing mothers.

Usage in Children: Safety of SINEMET in patients under 18 has not been established.

Precautions: As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide-angle glaucoma may be treated cautiously with SINEMET provided intraocular pressure is well controlled and patient is monitored carefully for changes in intraocular pressure during therapy.

Laboratory Tests: Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in protein-bound iodine, blood urea nitrogen, and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of SINEMET than with levodopa.

SINEMET may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions: Caution should be exercised when the following drugs are administered concomitantly with SINEMET.

Symptomatic postural hypotension can occur when SINEMET is added to the treatment of a patient receiving antihypertensive drugs. Therefore, when therapy with SINEMET is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS (above).

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and SINEMET.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET should be carefully observed for loss of therapeutic response.

Adverse Reactions: Most common serious adverse reactions occurring with SINEMET are choreiform, dystonic, and other involuntary movements. Other serious adverse reactions are mental changes including paranoid ideation and psychotic episodes, depression with or without development of suicidal tendencies and dementia. Convulsions also have occurred; however, a causal relationship with SINEMET has not been established.

A common but less serious effect is nausea.

Less frequent adverse reactions are cardiac irregularities and/or palpitation, orthostatic hypotensive episodes, bradykinetic episodes (the "on-off" phenomenon), anorexia, vomiting, and dizziness.

Rarely, GI bleeding, development of duodenal ulcer, hypertension, phlebitis, hemolytic and non-hemolytic anemia, thrombocytopenia, leukopenia, and agranulocytosis have occurred.

Laboratory tests which have been reported to be abnormal are alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, blood urea nitrogen, protein-bound iodine, and Coombs test.

Other adverse reactions that have been reported with levodopa are: *Nervous System*: ataxia, numbness, increased hand tremor, muscle twitching, muscle cramps, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome. *Psychiatric*: confusion, sleepiness, insomnia, nightmares, hallucinations, delusions, agitation, anxiety, euphoria. *Gastrointestinal*: dry mouth, bitter taste, sialorrhea, dysphagia, bruxism, hiccups, abdominal pain and distress, constipation, diarrhea, flatulence, burning sensation of tongue. *Metabolic*: weight gain or loss, edema. *Integumentary*: malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, skin rash, loss of hair. *Genitourinary*: urinary retention, urinary incontinence, dark urine, priapism. *Special Senses*: diplopia, blurred vision, dilated pupils, oculogyric crises. *Miscellaneous*: weakness, faintness, fatigue, headache, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

Overdosage: Management of acute overdosage with SINEMET is basically the same as management of acute overdosage with levodopa; however, pyridoxine is not effective in reversing the actions of SINEMET.

How Supplied: Tablets SINEMET 10-100, SINEMET 25-100, and SINEMET 25-250 are supplied in bottles of 100 and unit dose packages of 100.

Storage: Tablets SINEMET 10-100 and Tablets SINEMET 25-250 must be protected from light.

Manufactured by:
MERCK SHARP & DOHME
DIV OF MERCK & CO., INC.,
WEST POINT, PA 19486, USA

FOR:

DU PONT
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Sinemet®
(Carbidopa-Levodopa)

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INDEX TO ADVERTISERS

Berlex Imaging	604A-D
Du Pont Pharmaceuticals	Cover 2-558
Henry Ford Hospital	574
Geigy Pharmaceuticals	564A-B, 636A-B
Eli Lilly & Company	572A-D
Miles Pharmaceuticals	567-568
Parke-Davis	Cover 3-Cover 4
Sandoz Pharmaceuticals	571-572, 610-612
Wyeth-Ayerst Laboratories	559-560

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INDERAL® LA (propranolol HCl) Long Acting Capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION:
CONSULT THE PACKAGE LITERATURE FOR FULL PRESCRIBING INFORMATION.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Use beta blockers with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia; other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, thus abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, tachycardia was replaced by severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Use with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity resulting in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, as both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of significant drug-induced toxicity in rats or mice, employing doses up to 150 mg/kg/day over an 18-month period. There were no drug-related tumorigenic effects at any dosage levels. No impairment of fertility attributable to the drug was seen in animal reproductive studies.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Exercise caution when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. The oculomucocutaneous reactions associated with practolol have not been reported with propranolol.

DOSAGE AND ADMINISTRATION: INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

For management of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis the dosage must be individualized. Usual initial dose is 80 mg once daily.

If treatment is to be discontinued, reduce dosage gradually over a period of a few weeks (see WARNINGS).

PEDIATRIC DOSAGE – At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

OVERDOSAGE. INDERAL is not significantly dialyzable. If ingestion is, or may have been, recent, evacuate gastric contents, taking care to prevent pulmonary aspiration.

BRADYCARDIA: Administer atropine (0.25 to 1.0 mg); if no response to vagal blockade, administer isoproterenol cautiously. CARDIAC FAILURE: digitalization and diuretics. HYPOTENSION: vasopressors, eg, levarterenol or epinephrine (there is evidence that epinephrine is the drug of choice). BRONCHOSPASM: administer isoproterenol and aminophylline.

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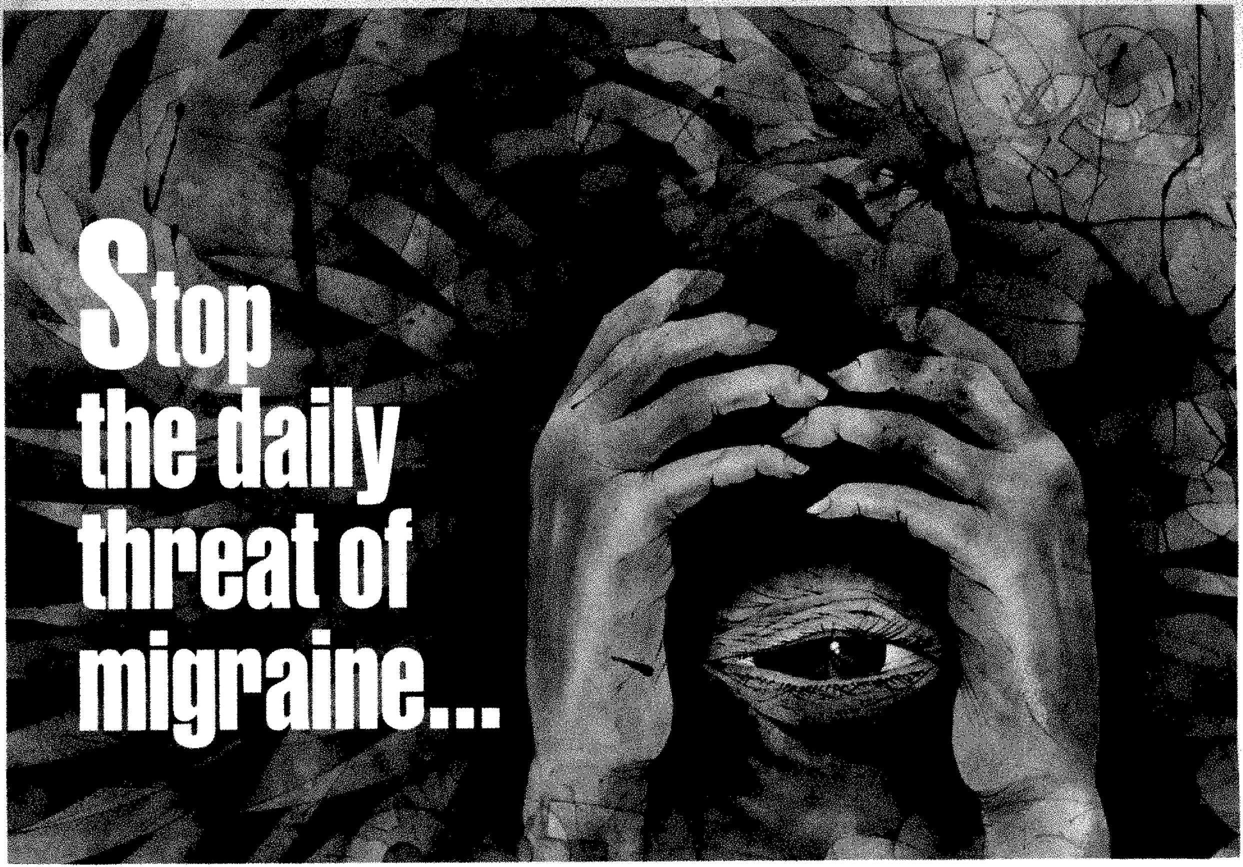
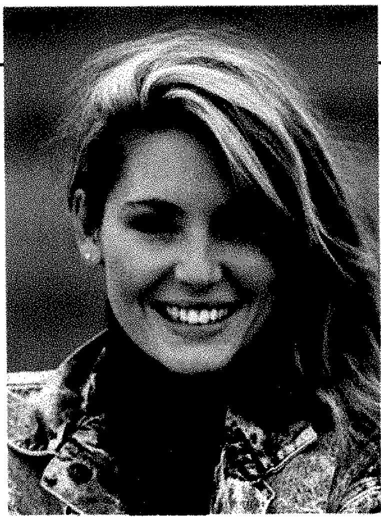


"Violent Passages" is a time-lapse portrayal by Louise Woodard depicting her own migraine headache sequence as she sees it. Her work focuses on the pain surrounding her eye and the confusion she feels as a result of the migraine.

with a daily dose of prevention.



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Proven qd prophylaxis at recommended doses.

Only INDERAL® LA provides once-daily preventive therapy— to significantly reduce both frequency and severity of common migraine. **Start with 80 mg/day and titrate to an effective dose — usually 160 to 240 mg once daily.**

Well-tolerated, long-term efficacy.

For patients whose day-to-day lives are undermined by anticipation of migraine, INDERAL LA can offer an improved sense of control. Because the only thing worse than the pain of migraine is the threat of it.

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INDERAL® LA
(PROPRANOLOL HCl)
LONG ACTING CAPSULES
60, 80, 120, 160 mg

Another day without migraine.

Please see next page for brief summary of prescribing information.

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Vol 48 No. 6 JUNE 1991

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Jurgen Kramer,
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P. M. Matthews, D. L. Arnold,
Reviewed by A. F. Haerer, MD, Jackson, Miss

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David A. Rottenberg,
Reviewed by Alexander Reeves, MD, Hanover, NH

The Cerebrospinal Fluid 566
Robert M. Herndon, Roger A. Brumback, (eds),
Reviewed by Robert J. Joynt, MD, PhD, Rochester, NY

LETTERS TO THE EDITOR

Effect of Chemotherapy on Glioma Metabolism 569
Howard S. Maker, MD, New York, NY

In Reply
Jack M. Rozental, MD, PhD, Ross L. Levine, MD, Madison, Wis

Post-Polio Fatigue Treated With Amantadine 570
Michael G. Dunn, MD, PhD, Rochester, NY

Machado-Joseph Disease or Not? 570
David M. Dawson, MD, West Roxbury, Mass

Continued on page 563.

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ARCHIVES

ORIGINAL CONTRIBUTIONS

A Comparison of Daily and Alternate-Day Prednisone Therapy in the Treatment of Duchenne Muscular Dystrophy 575
Gerald M. Fenichel, MD, Nashville, Tenn;
Jerry R. Mendell, MD, Columbus, Ohio;
Richard T. Moxley III, MD, Robert C. Griggs, MD, Rochester, NY;
Michael H. Brooke, MD, Edmonton, Alberta;
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Linda Signore, RN, MS, Columbus, Ohio;
Shree Pandya, MS, Rochester, NY;
Julaine Florence, MS; Janine Schierbecker, PT;
Bradley Wilson, St Louis, Mo

Vegetative State After Closed-Head Injury: A Traumatic Coma Data Bank Report 580
Harvey S. Levin, PhD; Christy Saydjari;
Howard M. Eisenberg, MD, Galveston, Tex;
Mary Foulkes, PhD, Bethesda, Md; Lawrence F. Marshall, MD,
Ronald M. Ruff, PhD, San Diego, Calif;
John A. Jane, MD, Charlottesville, Va;
Anthony Marmarou, PhD, Richmond, Va

The Influence of Gender on the Susceptibility to Multiple Sclerosis in Sibships 586
Adele D. Sadovnick, PhD, Vancouver, British Columbia;
Dennis E. Bulman; Lara Hashimoto, MS;
Marie B. D'Hooghe, MD; George C. Ebers, MD, London, Ontario

Incidence and Prevalence of Amyotrophic Lateral Sclerosis in Harris County, Texas, 1985-1988 589
John F. Annegers, PhD; Stanley Appel, MD; Ju Ruey-Jiuan Lee, MPH;
Penny Perkins, MPH, Houston, Tex

Estimated Prevalence of Dementia Among Elderly Black and White Community Residents 594
Albert Heyman, MD; Gerda Fillenbaum, PhD; Bea Prosnitz;
Kate Raiford, MSW; Bruce Burchett, PhD, Durham, NC;
Chris Clark, MD, Philadelphia, Pa

Association of Decreased Paternal Age and Late-Onset Alzheimer's Disease: An Example of Genetic Imprinting? 599
Lindsay A. Farrer, PhD; L. Adrienne Cupples, PhD; Linda Connor;
Philip A. Wolf, MD; John H. Growdon, MD, Boston, Mass

A 'Stress' Test for Memory Dysfunction: Electrophysiologic Manifestations of Early Alzheimer's Disease 605
Leyla deToledo-Morrell, PhD; Susan Evers;
Thomas J. Hoeppner, PhD; Frank Morrell, MD, MSc;
David C. Garron, PhD; Jacob H. Fox, MD, Chicago, Ill

Retrospective Postmortem Dementia Assessment: Validation of a New Clinical Interview to Assist Neuropathologic Study 613
Paula B. Davis, MD; Heidi White, MD; Joseph L. Price, PhD;
Daniel McKeel, MD; Lee N. Robins, PhD, St Louis, Mo

Continued on page 564.

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ARCHIVES

Neuropathologic and Neurochemical Correlates of Psychosis in Primary Dementia 619
George S. Zubenko, MD, PhD; John Moossy, MD; A. Julio Martinez, MD; Gutti Rao, MD; Diana Claassen, MD; Jules Rosen, MD; Ursula Kopp, Pittsburgh, Pa

Regional Cerebral Blood Flow After Human Cardiac Arrest: A Hexamethylpropyleneamine Oxime Single Photon Emission Computed Tomographic Study 625
Risto O. Roine, MD; Jyrki Launes, MD; Päivi Nikkinen, Lic Phil; Lena Lindroth, MSc; Markku Kaste, MD, Helsinki, Finland

Sclerosing Vasculopathy of the Central Nervous System in Nonelderly Demented Patients 631
Melinda L. Estes, MD, Cleveland, Ohio; Marc I. Chimowitz, MD, Ann Arbor, Mich; Norman B. Ratliff, MD; James T. McMahon, PhD; Anthony J. Furlan, MD; Issam A. Awad, MD, Cleveland, Ohio

Regional Cerebral Blood Flow Correlates of Language Processes in Reading Disability 637
D. Lynn Flowers, PhD; Frank B. Wood, PhD; Cecile E. Naylor, PhD, Winston-Salem, NC

Validation of a Clinical Antisaccadic Eye Movement Test in the Assessment of Dementia 644
Jon Currie, FRACP; Ben Ramsden; Cheryl McArthur; Paul Maruff, Parkville, Australia

HISTORY OF NEUROLOGY

Literary Neurologic Syndromes: Alice in Wonderland 649
Loren A. Rolak, MD, Houston, Tex

NEUROLOGICAL REVIEW

Central Nervous System Germinomas: A Review 652
Michael Bruce Horowitz, MD, Walter A. Hall, MD, Pittsburgh, Pa

OBSERVATION

Opercular Cheiro-oral Syndrome 658
Julien Bogousslavsky, MD; Karin Dizerens, MD; Franco Regli, MD; Paul-André Despland, MD, Lausanne, Switzerland

REGULAR DEPARTMENTS

Index to Advertisers 559

Calendar 565

Instructions for Authors 573

Classified Advertising 662

From refill to refill... which carbamazepine will your patient get next?

TEGRETOL is indicated for children 6 years and older and adults

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the following page, especially the boxed warning.

CIBA–GEIGY

Prevent substitution when you prescribe Tegretol

Sign each prescription on the line that prevents substitution, or add the phrase required in your state to prevent substitution:

☐ Dispense As Written
☐ No Substitution
☐ Do Not Substitute
☐ Brand Necessary
☐ No Drug Product Selection
☐ May Not Substitute
☐ Medically Necessary

For your Medicaid patients...

To prevent substitution of TEGRETOL for your Medicaid patients, be sure to add the phrase "Brand Medically Necessary" on each prescription.

Tegretol®
carbamazepine USP

200 mg scored tablets
100 mg chewable tablets

...because there's no substitute for experience.

Tegretol® carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink **Tablets of 200 mg—pink**

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION HOWEVER THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA

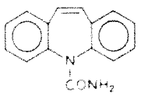
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME HOWEVER THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY NONETHELESS COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS. THE PATIENT SHOULD BE MONITORED CLOSELY DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol carbamazepine USP is an anticonvulsant and specific analgesic for trigeminal neuralgia available as chewable tablets of 100 mg and tablets of 200 mg for oral administration Its chemical name is 5H-dibenz [b f]azepine-5-carboxamide and its structural formula is



Carbamazepine USP is a white to off-white powder practically insoluble in water and soluble in alcohol and in acetone Its molecular weight is 236 27

Inactive Ingredients Colloidal silicon dioxide FD&C Red No 3 (chewable tablets only), FD&C Red No 40 (200-mg tablets only) flavoring (chewable tablets only) gelatin, glycerin magnesium stearate sodium starch glycolate (chewable tablets only), starch stearic acid, and sucrose (chewable tablets only)

CLINICAL PHARMACOLOGY

In controlled clinical trials Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia The mechanism of action remains unknown

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution thus avoiding undesirably high peak concentrations Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets Tegretol in blood is 76% bound to plasma proteins Plasma levels of Tegretol are variable and may range from 0 5-25 μg/ml, with no apparent relationship to the daily intake of the drug Usual adult therapeutic levels are between 4 and 12 μg/ml Following oral administration serum levels peak at 4 to 5 hours The CSF/serum ratio is 0 22 similar to the 22% unbound Tegretol in serum Because Tegretol may induce its own metabolism the half-life is also variable Initial half-life values range from 25-65 hours with 12-17 hours on repeated doses Tegretol is metabolized in the liver After oral administration of 14C-carbamazepine 72% of the administered radioactivity was found in the urine and 28% in the feces This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites with only 3% of unchanged Tegretol Transplacental passage of Tegretol is rapid (30 to 60 minutes) and the drug is accumulated in fetal tissues with higher levels found in liver and kidney than in brain and lungs

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types

1 Partial seizures with complex symptomatology (psychomotor temporal lobe) Patients with these seizures appear to show greater improvement than those with other types
2 Generalized tonic-clonic seizures (grand mal)
3 Mixed seizure patterns which include the above or other partial or generalized seizures

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS General)

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia

Beneficial results have also been reported in glossopharyngeal neuralgia

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression hypersensitivity to the drug or known sensitivity to any of the tricyclic compounds such as amitriptyline, desipramine, imipramine, protriptyline nortriptyline etc Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended Before administration of Tegretol MAO inhibitors should be discontinued for a minimum of fourteen days or longer if the clinical situation permits

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome have been reported with Tegretol These reactions have been extremely rare However, a few fatalities have been reported

Tegretol has shown mild anticholinergic activity, therefore, patients with increased intraocular pressure should be closely observed during therapy

Because of the relationship of the drug to other tricyclic compounds the possibility of activation of a latent psychosis and in elderly patients of confusion or agitation should be borne in mind

PRECAUTIONS

General: Before initiating therapy a detailed history and physical examination should be made

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE)

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever sore throat ulcers in the mouth easy bruising petechial or purpuric hemorrhage and should be advised to report to the physician immediately if any such signs or symptoms appear

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks

Laboratory Tests: Complete pretreatment blood counts including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops

Baseline and periodic evaluations of liver function particularly in patients with a history of liver disease must be performed during treatment with this drug since liver damage may occur The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

Baseline and periodic eye examinations including slit-lamp, funduscopy and tonometry are recommended since many phenothiazines and related drugs have been shown to cause eye changes

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance In addition measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used

Thyroid function tests have been reported to show decreased values with Tegretol administered alone

Hyponatremia has been reported in association with Tegretol use either alone or in combination with other drugs

Drug Interactions: The simultaneous administration of phenobarbital phenytoin or primidone or a combination of two, produces a marked lowering of serum levels of Tegretol The effect of valproic acid on Tegretol blood levels is not clearly established although an increase in the ratio of active 10 11-epoxide metabolite to parent compound is a consistent finding

The half-lives of phenytoin warfarin doxycycline and theophylline were significantly shortened when administered concurrently with Tegretol Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen

Concomitant administration of Tegretol with erythromycin cimetidine propoxyphene isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases Also concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25 75 and 250 mg/kg/day resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males

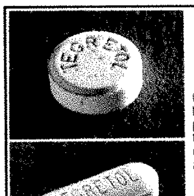
Carbamazepine must, therefore be considered to be carcinogenic in Sprague-Dawley rats Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results The significance of these findings relative to the use of carbamazepine in humans is at present, unknown

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg In rat teratology studies 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate 1 talipes 1 anophthalmos 2) In reproduction studies in rats nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations including spina bifida Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Retrospective case reviews suggest that compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy Therefore monotherapy is recommended for pregnant women

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient discontinuation of the drug may be considered prior to and during pregnancy although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown

Nursing Mothers: During lactation concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration

Because of the potential for serious adverse reactions in nursing infants from carbamazepine a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING) the skin and the cardiovascular system

The most frequently observed adverse reactions particularly during the initial phases of therapy are dizziness drowsiness unsteadiness nausea, and vomiting To minimize the possibility of such reactions therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

Hemopoietic System Aplastic anemia agranulocytosis pancytopenia bone marrow depression thrombocytopenia leukopenia leukocytosis eosinophilia acute intermittent porphyria

Skin Pruritic and erythematous rashes urticaria toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS) Stevens-Johnson syndrome (see WARNINGS) photosensitivity reactions, alterations in skin pigmentation exfoliative dermatitis erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus alopecia and diaphoresis In certain cases discontinuation of therapy may be necessary

Cardiovascular System Congestive heart failure edema aggravation of hypertension hypotension syncope and collapse aggravation of coronary artery disease arrhythmias and AV block primary thrombophlebitis recurrence of thrombophlebitis and adenopathy or lymphadenopathy

Some of these cardiovascular complications have resulted in fatalities Myocardial infarction has been associated with other tricyclic compounds

Liver Abnormalities in liver function tests cholestatic and hepatocellular jaundice hepatitis

Respiratory System Pulmonary hypersensitivity characterized by fever dyspnea pneumonitis or pneumonia

Genitourinary System Urinary frequency acute urinary retention oliguria with elevated blood pressure azotemia renal failure and impotence Albuminuria glycosuria elevated BUN and microscopic deposits in the urine have also been reported

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day Additionally rats receiving Tegretol in the diet for two years at dosage levels of 25 75 and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis In dogs it produced a brownish discoloration presumably a metabolite in the urinary bladder at dosage levels of 50 mg/kg and higher Relevance of these findings to humans is unknown

Nervous System Dizziness drowsiness disturbances of coordination, confusion headache fatigue blurred vision visual hallucinations transient diplopia oculomotor disturbances nystagmus, speech disturbances, abnormal involuntary movements peripheral neuritis and paresthesias, depression with agitation talkativeness tinnitus and hyperacusis

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency but the exact relationship of these reactions to the drug has not been established

Digestive System Nausea, vomiting gastric distress and abdominal pain diarrhea constipation anorexia and dryness of the mouth and pharynx including glossitis and stomatitis

Eyes Scattered punctate cortical lens opacities as well as conjunctivitis have been reported Although a direct causal relationship has not been established many phenothiazines and related drugs have been shown to cause eye changes

Musculoskeletal System Aching joints and muscles and leg cramps

Metabolism Fever and chills inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported Cases of frank water intoxication with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS Laboratory Tests)

Other Isolated cases of a lupus erythematosus-like syndrome have been reported There have been occasional reports of elevated levels of cholesterol HDL cholesterol and triglycerides in patients taking anticonvulsants

A case of aseptic meningitis accompanied by myoclonus and peripheral eosinophilia has been reported in a patient taking carbamazepine in combination with other medications The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol nor is there evidence of psychological or physical dependence in humans

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose adults, >60 g (39-year-old man) Highest known doses survived adults 30 g (31-year-old woman) children 10 g (6-year-old boy) small children 5 g (3-year-old girl)

Oral LD 50 in animals (mg/kg) mice, 1100-3750 rats, 3850-4025, rabbits 1500-2680, guinea pigs, 920

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours Neuromuscular disturbances are the most prominent Cardiovascular disorders are generally milder and severe cardiac complications occur only when very high doses (>60 g) have been ingested

Respiration Irregular breathing respiratory depression

Cardiovascular System Tachycardia, hypotension or hypertension shock, conduction disorders

Nervous System and Muscles Impairment of consciousness ranging in severity to deep coma Convulsions especially in small children Motor restlessness muscular twitching tremor, athetoid movements opisthotonos, ataxia drowsiness dizziness mydriasis nystagmus adiadochokinesia ballism psychomotor disturbances dysmetria initial hyperreflexia followed by hyporeflexia

Gastrointestinal Tract Nausea, vomiting

Kidneys and Bladder Anuria or oliguria, urinary retention

Laboratory Findings Isolated instances of overdosage have included leukocytosis reduced leukocyte count glycosuria and acetonuria EEG may show dysrhythmias

Combined Poisoning When alcohol, tricyclic antidepressants barbiturates or hydantoins are taken at the same time the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug which may be achieved by inducing vomiting irrigating the stomach and by taking appropriate steps to diminish absorption If these measures cannot be implemented without risk on the spot the patient should be transferred at once to a hospital while ensuring that vital functions are safeguarded There is no specific antidote

Elimination of the Drug Induction of vomiting

Gastric lavage Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated especially if the patient has also consumed alcohol

Measures to Reduce Absorption Activated charcoal, laxatives

Measures to Accelerate Elimination Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure Replacement transfusion is indicated in severe poisoning in small children

Respiratory Depression Keep the airways free, resort, if necessary, to endotracheal intubation artificial respiration and administration of oxygen

Hypotension Shock Keep the patient's legs raised and administer a plasma expander If blood pressure fails to rise despite measures taken to increase plasma volume use of vasoactive substances should be considered

Convulsions Diazepam or barbiturates

Warning Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension and coma However barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week)

Surveillance Respiration cardiac function (ECG monitoring), blood pressure, body temperature pupillary reflexes and kidney and bladder function should be monitored for several days

Treatment of Blood Count Abnormalities If evidence of significant bone marrow depression develops the following recommendations are suggested (1) stop the drug (2) perform daily CBC platelet and reticulocyte counts (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery

Special periodic studies might be helpful as follows (1) white cell and platelet antibodies (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units (6) hemoglobin electrophoresis for A_2 and F hemoglobin and (7) serum folic acid and B_{12} levels

A fully developed aplastic anemia will require appropriate intensive monitoring and therapy for which specialized consultation should be sought

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS Laboratory Tests) Dosage should be adjusted to the needs of the individual patient A low initial daily dosage with a gradual increase is advised As soon as adequate control is achieved the dosage may be reduced very gradually to the minimum effective level Tablets should be taken with meals

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b i d Increase at weekly intervals by adding up to 200 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age Doses up to 1600 mg daily have been used in adults in rare instances ***Maintenance***: Adjust dosage to the minimum effective level usually 800-1200 mg daily

Children 6-12 years of age—Initial: 100 mg b i d Increase at weekly intervals by adding 100 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg ***Maintenance***: Adjust dosage to the minimum effective level usually 400-800 mg daily

Combination Therapy: Tegretol may be used alone or with other anticonvulsants When added to existing anticonvulsant therapy the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased except phenytoin which may have to be increased (see PRECAUTIONS Drug Interactions and Pregnancy Category C)

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b i d on the first day for a total daily dose of 200 mg This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain Do not exceed 1200 mg daily

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily However some patients may be maintained on as little as 200 mg daily while others may require as much as 1200 mg daily At least once every 3 months throughout the treatment period attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug

HOW SUPPLIED

Chewable Tablets 100 mg—round red-speckled pink single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit 12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100 (strips of 10)	NDC 0028-0027-61

Samples when available are identified by the word *SAMPLE* appearing on each tablet

Protect from moisture

Dispense in tight container (USP)

Also available as Tegretol suspension 100 mg/5 ml in 450 ml bottles

Printed in U S A C90-34 (Rev 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

Calendar

CALENDAR OF MEETINGS

1991

May	30-June 1	International Conference on Stroke, Geneva, Switzerland. Contact N. M. Bornstein, MD, International Conference on Stroke, c/o Kuoni Travel Ltd, 7 Rue de Berne, CH-1211 Geneva, Switzerland.
June	1-6	The 15th International Symposium on Cerebral Blood Flow and Metabolism, James L. Knight International Center, Miami, Fla. Contact Ms Jenny Bernal, Conference Coordinator, Brain '91, University of Miami Conference Center, 400 SE Second Ave, Fourth Floor, Miami, FL 33131.
	2-6	Ninth International Congress of Electromyography, Jerusalem, Israel. Contact Dr Arieh N. Gilai, Convener, EMG-CN-IX Congress, PO Box 29334, Tel Aviv 61292, Israel.
	5-7	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," Schuss Mountain Resort, Mancelona, Mich. Contact Susan Mitchell, EdD, 2929 Race St, Forth Worth, TX 76111; (817) 831-2604.
	7	"Neuro-Ophthalmology 1991," Cleveland, Ohio. Contact John Rus, Office of Continuing Medical Education, 2109 Adelbert Rd, W-175, Cleveland, OH 44106; (216) 368-2409.
	10-13	Twelfth Annual Child Neurology Postgraduate Course, Sonesta Beach Hotel, Key Biscayne, Fla. Contact Oscar Papazian, MD, Department of Neurology, Miami Children's Hospital, 3200 SW 60th Ct, Miami, FL 33155; (305) 662-8330.
	16-21	Seventh International Conference on the Acquired Immunodeficiency Syndrome, Florence, Italy. Contact Christina D'Addazio, Laboratory of Virology, Istituto Superiore di Sanitá, Viale Regina Elena 299, 00161 Rome, Italy.
	19-22	The 26th Annual Meeting of the Canadian Congress of Neurological Sciences, Halifax (Nova Scotia) Sheraton. Contact Permanent Secretariat, Canadian Congress of Neurological Sciences, 810-906 12th Ave SW, Calgary, Alberta, Canada T2R 1K7; (403) 229-9544.
	21-23	"Current Concepts in Child Neurology," Hyatt Islandia Hotel, San Diego, Calif. Contact Continuing Medical Education, Children's Hospital and Health Center, 8001 Frost St, San Diego, CA 92123; (619) 576-1700.
	20-23	The 66th Annual Meeting of the American Association of Neuropathologists, Omni Innerharbor Hotel, Baltimore, Md. Contact Reid R. Heffner, Jr, MD, Department of Pathology, 204 Farber Hall, State University of New York at Buffalo School of Medicine, Buffalo, NY 14214; (716) 898-3114.
	23-29	Ninth European Congress of Neurosurgery, Moscow, Union of Soviet Socialist Republics. Contact Organizing Committee, Ninth European Congress of Neurosurgery, 5 Fadeev St, Moscow 125047, Union of Soviet Socialist Republics.
	26-28	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," The Snowmass Conference Center, Snowmass Village, Colo. Contact Susan Mitchell, EdD, 2929 Race St, Forth Worth TX 76111; (817) 831-2604.
	27-29	"Clinical Neuro-Oncology Update," Towsley Center, Ann Arbor, Mich. Contact Julie Jacobs, Towsley Center for Continuing Medical Education, Department of Postgraduate Medicine, The University of Michigan Medical School, PO Box 1157, Ann Arbor, MI 48106-9869; (313) 763-1400.
	29-July 3	Fifth International Headache Congress, Washington, DC. Contact the Fifth International Headache Congress, 22 Euclid St, Woodbury, NJ 08096; (609) 845-7220.
July	1-5	Third Meeting of the International Neurotoxicology Association, Parma, Italy. Contact Dr A. Mutti, Organizing Secretary, Laboratory of Industrial Toxicology, University of Parma, Via Gramsci 14, I-43100, Parma, Italy.
	7-10	23rd Annual March of Dimes Clinical Genetics Conference, Vancouver, British Columbia. Contact March of Dimes, 1275 Mamaroneck Ave, White Plains, NY 10605; (914) 428-7100.
	10-13	International Workshop on Huntington's Disease, Cardiff, Wales. Contact Professor P. S. Harper, Institute of Medical Genetics, University of Wales College of Medicine, Heath Park, Cardiff, CF4 4XN, Wales.
	15-19	14th Annual Contemporary Clinical Neurology Symposium, The Conference Center at Palmetto Dunes Resort, Hilton Head Island, SC. Contact Marsha Bain, Vanderbilt Division of Continuing Medical Education, D-8211 Medical Center North, Nashville, TN 37232-2337; (615) 322-4030.
August	7-9	"Modern Dissection Techniques of Bone, Biometals, Bioceramics, and Bioplastics," Sheraton Inn and Conference Center, Worcester, Mass. Contact Susan Mitchell, EdD, 2929 Race St, Forth Worth, TX 76111; (817) 831-2604.
	14-18	The Second Dartmouth International Conference on the Corpus Callosum and Epilepsy, Dartmouth-Hitchcock Medical Center, Hanover, NH. Contact Alexander G. Reeves, MD, Section of Neurology, Dartmouth-Hitchcock Medical Center, Hanover, NH 03756.
	27-30	Fourth International Tinnitus Seminar, Bordeaux, France. Contact Jean-Marie Aran, Unité Institut National de la Santé et de la Recherche Médicale 229, Audiologie Expérimentale Hôpital Pellegrin, Place Amélie-Raba-Léon, 33076 Bordeaux Cedex, France.

Books

Intervertebral Disk Disease: Causes, Diagnosis, Treatment, and Prophylaxis, ed 2, by Jurgen Kramer, 312 pp, New York, NY, Thieme Medical Publishers Inc, 1990.

This book, translated from the original German-language text, is one that is quite comprehensive, well written, and organized. The early chapters in the book are devoted to the basic sciences relevant to intervertebral disk disorders. The chapters on anatomy and physiology, biomechanics, and pathology are quite detailed, with very extensive scientific references. The chapter on the thoracic syndrome is very short, but the chapters on cervical and lumbar syndromes cover their subject matter well, with excellent descriptions of the clinical presentations related to specific pathologic processes. Newer imaging techniques in the evaluation of intervertebral disorders are described. Nonoperative and operative management and rehabilitation methods are well described. The concluding chapters deal with the psychological problems of patients with spine syndromes. The book concludes with a chapter on general rehabilitation and prevention. Most chapters are well illustrated with good diagrams and photographs. It makes for easy reading and is recommended for any physician who has to deal with problems related to the spine.

Donald P. K. Chan, MD
Rochester, NY

Diagnostic Tests in Neurology, by P. M. Matthews and D. L. Arnold, 372 pp, $39.95, New York, NY, Churchill Livingstone Inc, 1991.

Technological advances continue to improve our ability to study the healthy and diseased nervous system in the laboratory. The authors, along with four contributors, have written a small, soft-covered text devoted to diagnostic tests in neurology. This book is not intended as a textbook of neurology, and the authors point to the primacy of obtaining a history and performing an examination in neurologic diagnosis.

The book is divided into two sections. Section 1 is said to be at the level of a junior resident in neurology. It includes chapters dealing with lumbar puncture and cerebrospinal fluid, neuroradiology, ultrasound, evoked potentials, electromyography and electroencephalography, biopsies, and tests for hereditary metabolic diseases. These chapters begin with very elementary descriptions of each diagnostic test. Their coverage is somewhat uneven, but one can argue about the depth of knowledge of the various tests expected of a junior resident in neurology. Illustrations are included mainly in the chapters on imaging procedures. While appropriate, the figures are not as well reproduced as one might wish.

Section 2, "Diagnostic Approaches to Common Neurologic Problems," is organized in 10 chapters. Laboratory studies appropriate for the study of patients with seizures, coma, dementia, focal deficits, and other clinical categories are presented in more detail. Section 2 is replete with lists and tables, some quite exhaustive. The tables present the differential diagnosis of various neurologic conditions as perceived by the authors and suggest laboratory studies to arrive at the definitive diagnosis. Some lists are more detailed than others; many are quite current and useful, an example being the chapter that deals with the various coagulopathies.

One can argue with some of the titles: on page 52 one finds a section on "Cardiac Echocardiography."

Overall, this is a useful volume for the neurologic house officer and for the practicing neurologist.

A. F. Haerer, MD
Jackson, Miss

Neurological Complications of Cancer Treatment, by David A Rottenberg, 228 pp, $59.95, Stoneham, Mass, Butterworth Publishers Inc, 1991.

This is a fine, multiauthored monograph answering the need for a readily available reference on the neurological side effects of radiation and chemotherapy. The clinical presentation and pathophysiology of the various peripheral and central nervous system side effects of radiation and chemotherapy for malignancy are well covered. With the exception of an extensive chapter on arterial chemotherapy for central nervous system malignancy, an experimental modality limited by unacceptable side effects, the book appropriately covers all practical modalities of cancer therapy. There is a modicum of inevitable redundancy, which improves the value of each chapter as a single resource on the specific modality reviewed. The bibliographies are extensive.

This book is highly recommended for all physicians who are involved with the care of cancer patients.

Alexander Reeves, MD
Hanover, NH

The Cerebrospinal Fluid, edited by Robert M. Herndon and Roger A. Brumback, 306 pp, $110, Norwell, Mass, Kluwer Academic Publishers, 1989.

"A spinal tap! What for? We have the MRI, CT, EEG, EMG, SEP, MMPI, and I even did a history and physical. Just what can we learn from the CSF?" A familiar conversation with the house staff—just give them this book.

There has not been a good book on spinal fluid for many years. This likely reflects our distraction in high-technology brain imaging procedures. We have neglected one of the best diagnostic methods easily available to us.

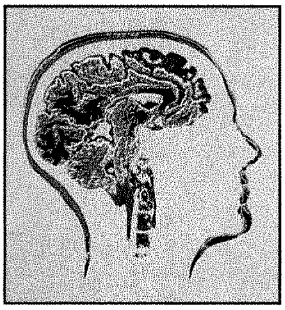
There are 11 chapters, with the major contributions by the two editors. They cover history, anatomy and physiology, production and flow, collection, injection, infections, proteins, immunology, cytology, and cytopathology. The authors are all experienced clinicians so that theory is introduced as it relates to clinical problems. The illustrations are excellent and the color plates are superb. The chapters on cytopathology illustrate the potential diagnostic possibilities offered by examination of the spinal fluid.

House staff should take time off from writing requisitions for various tests and read this to see what potential for diagnosis is the length of a needle away.

"Just get the spinal fluid, dammit!"

Robert J. Joynt, MD, PhD
Rochester, NY

THROUGH A CALCIUM-MODULATING MECHANISM OF ACTION



CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

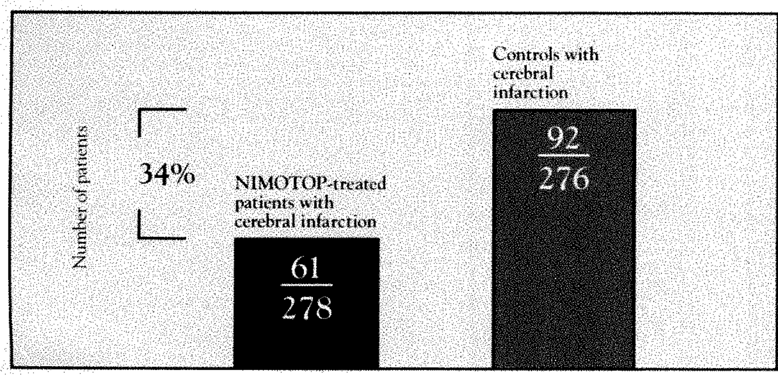
CAPSULES 30 mg

REDUCES INCIDENCE OF CEREBRAL INFARCTION IN PATIENTS FOLLOWING SUBARACHNOID HEMORRHAGE

In the largest study to date, NIMOTOP demonstrated a significant reduction in incidence of cerebral infarction[1]

- Twenty-two percent (61/278) of NIMOTOP-treated patients experienced cerebral infarction vs. 33% (92/276) of controls
- NIMOTOP reduced the incidence of cerebral infarction by 34%

Thirty-four percent reduction in incidence of cerebral infarction with NIMOTOP-treated patients vs. controls (n=554; p=0.003)[1]*



*90% of patients in this study were Hunt and Hess Grades I-III.

Dose: 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 days commencing within 96 hours of SAH.

Adapted from Pickard, et al.[1]

NIMOTOP modulates calcium influx to promote cerebral perfusion, and may directly protect neurons[2-5]

"[In animals] The beneficial cytoprotective effect of nimodipine, probably related to normalization of calcium homeostasis and blood-brain barrier permeability after ischemia, may reflect both vascular and cellular sites of action."[6]

Lazarewicz JW, et al. *Stroke* 1989.

"[In humans] The data thus suggest that nimodipine neither prevents nor reverses cerebral vasospasm. Calcium channel blockers such as nimodipine may have an effect on cerebral arterioles that are below the limits of resolution of angiography. . . ."[1]

Pickard JD, et al. *Br Med J* 1989.

Please see references and Brief Summary of full prescribing information on next page.

MILES

CEREBROSELECTIVE
NIMOTOP®
nimodipine/Miles
CAPSULES 30 mg

NIMOTOP REDUCES THE INCIDENCE OF CEREBRAL INFARCTION FOLLOWING SUBARACHNOID HEMORRHAGE

BRIEF SUMMARY
NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

MILES

Manufactured by: **Miles Inc.**
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Encapsulated by: **R.P. Scherer North America**
Division of R.P. Scherer Corp.
Clearwater, FL 33518

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REFERENCES
1. Pickard JD, Murray GD, Illingworth R, et al. *Br Med J.* 1989;298:636-642. **2.** Solomon RA, Fink ME. *Arch Neurol.* 1987;44:769-773. **3.** Petruk KC, West M, Mohr G, et al. *J Neurosurg.* 1988;68:505-517. **4.** Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. *Acta Neurol Scand.* 1987;76:267-271. **5.** Scriabine A, van den Kerckhoff W. *Ann NY Acad Sci.* 1988;522:698-706. **6.** Lazarewicz JW, Pluta R, Salinska E, Puka M. *Stroke.* 1989;20:70-77.

Miles Inc.
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West Haven, CT 06516
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Letters to the Editor

Letters to the editor should be submitted as an original and two duplicates. They should be typewritten double-spaced on plain bond paper; they will be subject to editing. If they are prepared on a word processor, do not justify the right margin. A copyright transmittal letter signed by all authors must accompany this (see "Instructions for Authors").

Effect of Chemotherapy on Glioma Metabolism

To the Editor.—Rozental et al[1] reported the effect of chemotherapy on the uptake of fluorodeoxyglucose F18 into human gliomas determined by positron emission scanning. They confirmed previous reports that glucose uptake correlates with the histological degree of malignancy and, as had others, attributed the increased uptake to an intrinsically high aerobic glycolytic rate in tumors. Although it is true that most neoplastic cells have a higher rate of aerobic glycolysis (metabolism when fully oxygenated) than their nonneoplastic cells of origin[2]; it is doubtful that the metabolism of malignant gliomas is truly aerobic. Several years ago we noted that the metabolic enzyme profiles of several experimental neoplasms did suggest a high glycolytic capacity,[3] but that changes in glucose, lactate, and high-energy phosphates during ischemia in an experimental ependymoblastoma implanted in mouse brain indicated that the tumors functioned at less than adequate oxygen levels.[4,5] Indeed, the high levels of glycolytic enzymes may be partly an adaptation to a low oxygen environment.[6] In addition, the edema that is variably present may increase glucose metabolism in the absence of neoplastic cells.[7] The larger the neoplasm the greater the evidence of ischemia.[5] The high glucose uptake of malignant tumors may be largely dependent on their tendency to outgrow their supply of oxygen relative to that of glucose, inducing an increase in glucose uptake by the deregulation of glycolysis (Pasteur effect).[8,9] Microchemical measurements showing a gradient of metabolism, becoming more anaerobic with distance from supplying vessels,[8] support the importance of circulatory factors in determining the mode of metabolism.

Thymidine incorporation into cellular DNA, a marker of cell proliferation, was significantly greater in perivascular regions of a C6 neoplasm growing in mouse brain than in more poorly supplied deeper regions.[10] Following the administration of lomustine (CCNU), depressed thymidine incorporation recovered earlier in areas closer to capillaries than peripherally, although these regions had been exposed to higher concentrations of the agent. In monolayer culture, better oxygenated isolated C6 glioma cells were more vulnerable to nitrosourea damage than were confluent cells; vulnerability was inversely related to cell density.[11] Rozental et al[1] found increased fluorodeoxyglucose uptake (measured as tumor/white matter ratio) into several human gliomas 24 hours after chemotherapy and suggested that a direct metabolic effect may have occurred. Alternatively, a greater vulnerability to chemotherapy of cells infiltrating normal brain, close to vessels and with higher rates of proliferation and lower rates of "aerobic" glycolysis because of a better oxygen supply, could have contributed to the pattern of metabolic change found by positron emission tomographic scanning following treatment of the tumors by leaving a surviving cell population less well supplied with oxygen.

Howard S. Maker, MD
Department of Neurology
Mt Sinai School of Medicine
Beth Israel Medical Center
1st Avenue at 16th Street
New York, NY 10003

1. Rozental JM, Levine RL, Nickles RJ, Dobkin JA. Glucose uptake by gliomas after treatment. *Arch Neurol.* 1989;46:1302-1307.
2. Mangiardi JR, Yodice P. Metabolism of the malignant astrocytoma. *Neurosurgery.* 1990;26:1-11.
3. Lehrer GM, Maker HS, Silides DJ, Weiss C, Scheinberg LC. The quantitative histochemistry of a chemically induced ependymoblastoma; I: enzymes. *J Neurochem.* 1966;13:1197-1206.
4. Maker HS, Lehrer GM, Weiss C, Silides DJ, Scheinberg LC. The quantitative histochemistry of a chemically induced ependymoblastoma; II: the effect of ischemia on substrates of carbohydrate metabolism. *J Neurochem.* 1966;13:1207-1212.
5. Maker HS, Lehrer GM, Silides DJ, Weiss C. Circulatory factors in the carbohydrate metabolism of an experimental glial neoplasm. *Ann N Y Acad Sci.* 1969;159:273-275.
6. Maker HS, Lehrer GM, Weissbarth S, Bornstein MB. Changes in LDH isoenzymes of brain developing in situ and in vitro. *Brain Res.* 1972;44:189-196.
7. Sutton LN, Barranco D, Greenberg J, Dante S, Florin S, Welsh F. Cerebral blood flow and glucose metabolism in experimental brain edema. *J Neurosurg.* 1989;71:868-874.
8. Maker HS, Lehrer GM. Environmental factors in the structure, metabolism and growth of glial tumors. In: Paoletti EG, Kirsch W, Paoletti F, eds. *Experimental Biology of Brain Tumors.* Springfield, Ill: Charles C Thomas Publisher; 1972:519-532.
9. Vaupel P, Kallinowski F, Okunieff P. Blood flow, oxygen and nutrient supply and metabolic microenvironment of human tumors: a review. *Cancer Res.* 1989;49:6449-6465.
10. Maker HS, Syed H, Whetsell W, Lehrer GM. Environmental factors modifying the effect of CCNU on glioma in vitro and in vivo. *Trans Am Neurol Assoc.* 1976;101:272-275.
11. Maker HS, Syed HH, Lehrer GM. Environmental factors in glial tumor response to CCNU. *J Natl Cancer Inst.* 1977;59:1427-1429.

In Reply.—In his letter to the editor, Maker raises an interesting issue regarding our article "Glucose Uptake by Gliomas After Treatment."[1] Maker states that tumor cells in a well-oxygenated environment (closer to blood vessels) tend to be more vulnerable to chemotherapy. Thus, tumor cells in a relatively hypoxic environment would be more likely to survive treatment. Furthermore, the rate of glucose uptake by tumor cells increases and becomes deregulated with increasing hypoxia (increasing distance from blood vessels). Therefore, if hypoxic cell populations predominate following exposure to chemotherapy, glucose uptake would appear to increase relative to the baseline state.

This alternative explanation for the increase in glucose uptake observed after chemotherapy was only briefly considered in our discussion for several reasons. We stated that the phenomenon "... might have originated from the chemoresistant (ie, also hypoxic) subpopulation of cells, it could represent a mechanism for synchronization, release from growth arrest, and tumor overgrowth following ineffective chemotherapy." We felt that although a proportion of cells had surely accumulated a lethal amount of damage, a 24-hour interval from treatment was too short a period of time for the damaged cells to die. Even if such acute cell death occurred, one would expect a decrease from the baseline of *average* tumor metabolism simply because a group of metabolically active cells within the tumor volume had been eliminated. In other words, even though only hypoxic, "hypermetabolic" cells were left after the chemical debulking, fewer cells remained in the same volume. Otherwise, a collapse or structural rearrangement of the tumor must have taken place to account for an increase in glucose uptake within a region of interest of the same size taken from the same place on baseline and follow-up positron emission tomographic scans. Neither positron emission tomographic scans, computed tomographic scans, or magnetic resonance imaging give evidence of structural rearrangements within tumors at such an early interval following treatment.

It must also be pointed out that certain tumor models are capable of reenergizing (increasing their levels of nucleoside triphosphates and phosphocreatine) after treatment.[2] In that regard, at 4 days after treatment, a subcutaneous gliosarcoma reenergizes, shows a larger proportion of viable cells, and demonstrates a fivefold increase in interstitial space compared with the control tumor.[3] At this time, we can only speculate regarding the nature of our observation. It may reflect the first step in reenergization, increased energy requirements for repair, or incipient repopulation from a hypoxic cell pool (as Maker suggests).

We appreciate Maker's thought-provoking comments.

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1. Rozental JM, Levine RL, Nickles RJ, Dobkin JA. Glucose uptake by gliomas after treatment: a positron emission tomographic study. *Arch Neurol.* 1989;46:1302-1307.
2. Steen RG. Response of solid tumors to chemotherapy monitored by in vivo ^{31}P nuclear magnetic resonance spectroscopy: a review. *Cancer Res.* 1989;49:4075-4085.
3. Steen RG, Tamargo RJ, McGovern KA, et al. In vivo ^{31}P nuclear magnetic resonance spectroscopy of subcutaneous 9L gliosarcoma: effects of tumor growth and treatment with 1,3-*bis*(2-chloroethyl)-1-nitrosourea on tumor bioenergetics and histology. *Cancer Res.* 1988;48:676-681.

Post-Polio Fatigue Treated With Amantadine

To the Editor.—The post-polio syndrome (PPS) has received increased attention in recent years. This is a chronic slowly progressive condition with cardinal features consisting of weakness, atrophy, aches, cramps, and fatigue decades after the initial infection. Fatigue may be an incapacitating feature of this illness.

Amantadine has been found to be beneficial in the fatigue of multiple sclerosis.[1,2] The basis for this is uncertain. Amantadine also possesses antiviral and antiparkinsonian effects.

Average Daily Fatigue (Scale: 1 to 10)

Patient	Week 1	2	3*	4	5
1	5.4	7.2	5.3	4.2	5.0
2	7.8	7.0	6.5	7.1	6.5
3	5.7	7.6	1.8	2.2	. . .
4	4.4	3.2	3.0	3.0	2.3
5	5.4	5.4	5.6†	4.4	3.0
6	8.6	6.4‡	5.2	4.7	. . .
7	6.4	6.4	5.6	5.6	. . .
8	8.1	7.1	6.4	5.4§	. . .
9	7.3	7.1	6.6	7.1§	. . .

*Began treatment with amantadine.
†Upper respiratory illness.
‡Began treatment with amantadine after 1 week.
§Discontinued medication.

Over the last year an open study of amantadine (100 mg two times a day) given for the fatigue of PPS has been carried out in nine patients. All patients had PPS as diagnosed by a combination of accepted criteria, including history, physical examination, and electrodiagnostic testing, where applicable. The study used a 2-week control period with daily self-rating of fatigue on a subjective 0 (no fatigue) to 10 (incapacitating fatigue) scale. Treatment with amantadine (100 mg two times a day) was then begun. Eight of nine patients noted a subjective improvement in fatigue, and seven desired to stay on the medication (Table).

The degree of benefit is quite variable. Some patients appear to have little improvement, but still noted enough improvement to desire continued therapy (ie, patient 2). Others noted a dramatic difference (ie, patient 3). One patient left the study due to side effects and is not included in the Table. In one patient, the fatigue returned to prestudy baseline when the medication was discontinued after several months, and the beneficial effect of amantadine was reproduced when treatment was reinstituted.

This small study shows a trend toward reduction of fatigue in PPS with the use of amantadine. This may represent a significant advance in symptomatic treatment of this condition, as no other therapeutic modalities currently exist. A blinded placebo-controlled study would be appropriate based on these preliminary findings.

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1. Murray TJ. The treatment of fatigue in MS. *Neurology.* 1984;34(suppl 1):139.
2. Rosenberg GA, Appenzeller O. Amantadine, fatigue, and multiple sclerosis. *Arch Neurol.* 1988;45:1104-1106.

Machado-Joseph Disease or Not?

To the Editor.—Eto and coworkers[1] describe 12 patients with a hereditary ataxia they believe most closely resembles spinopontine atrophy as described by Boller and Segarra[2] in a large Rhode Island kindred, the family W, of English extraction. I have had contact with this family. One patient from the family actually appears in the literature twice, as patient 2 in the report on spinopontine atrophy by Pogacar et al,[3] and again as a patient with olivopontocerebellar atrophy in the writings of Huang and Plaitakis.[4] The distinctions between spinopontine atrophy and olivopontocerebellar atrophy seem slight indeed on clinical or pathologic grounds.

Eto et al[1] compare spinopontine atrophy to Machado-Joseph disease and note the many similarities. Machado-Joseph disease is distinctive primarily in its geographic source. Many hundreds of patients and nonaffected family members of Azorean lineage have been examined, and cultured cell lines established from those individuals who must surely represent a genetically homogeneous condition. Discovery of the gene seems only a matter of time (P. McLeod, personal communication). "Non-Azorean Machado-Joseph disease" is a term of little meaning until the genetic locus of Machado-Joseph disease, and of its non-Azorean wannabees, is worked out.

The family W, whether having olivopontocerebellar atrophy or spinopontine atrophy, represents a comparable opportunity for genetic analysis.

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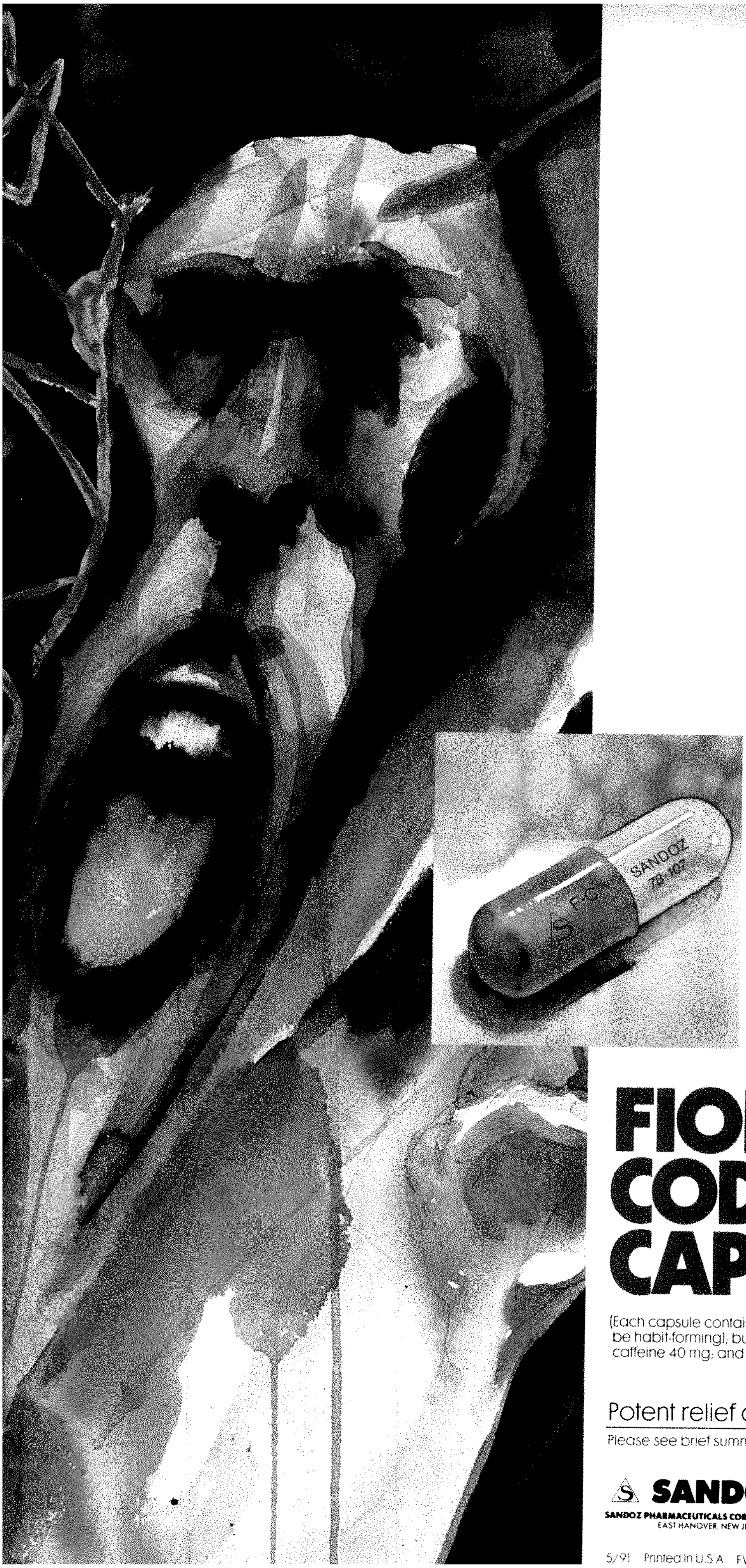
1. Eto K, Sumi M, Bird TD, et al. Family with dominantly inherited ataxia, amyotrophy, and peripheral sensory loss: spinopontine atrophy or Machado-Joseph Azorean disease in another non-Portuguese family? *Arch Neurol.* 1990;47:968-977.
2. Boller F, Segarra JM. Spinopontine degeneration. *Eur Neurol.* 1979;2:356-373.
3. Pogacar S, Ambler M, Conklin WJ, et al. Dominant spinopontine atrophy: report of two additional members of family W. *Arch Neurol.* 1978;35:136-162.
4. Huang YP, Plaitakis A. Morphological changes of olivopontocerebellar atrophy in computed tomography and comments on its pathogenesis. *Adv Neurol.* 1984;41:39-87.



HEADACHE DESCRIBED

"Headache"– a personal interpretation of headache pain by John Crowley, a headache patient.

HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL® WITH CODEINE CAPSULES Ⓒ III

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming], caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

SANDOZ

SANDOZ PHARMACEUTICALS CORPORATION
EAST HANOVER, NEW JERSEY 07936

5/91 Printed in U.S.A. FWC-1290-01

BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming]; butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Placebo (N = 377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus; hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

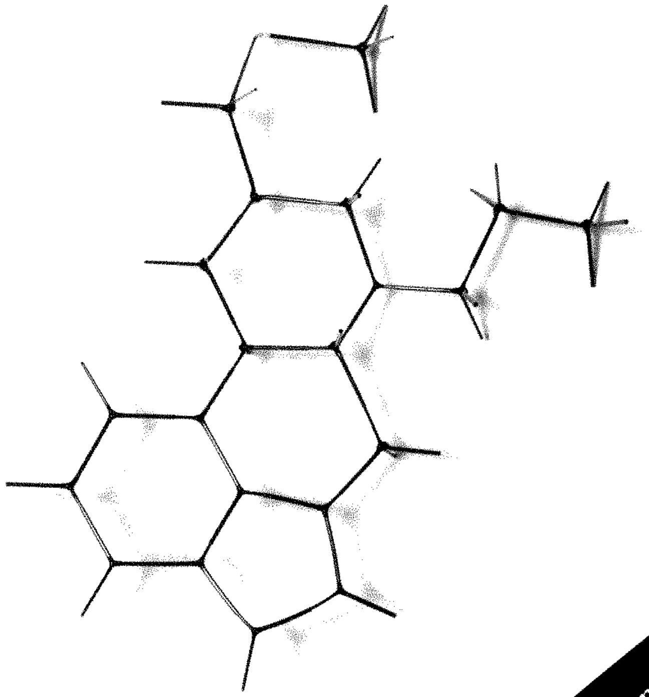
Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

(NOVEMBER 1, 1990 · FWC-Z26)

PERMAX®
pergolide mesylate

An adjunct to levodopa/carbidopa treatment
in the management of patients
with Parkinson's disease



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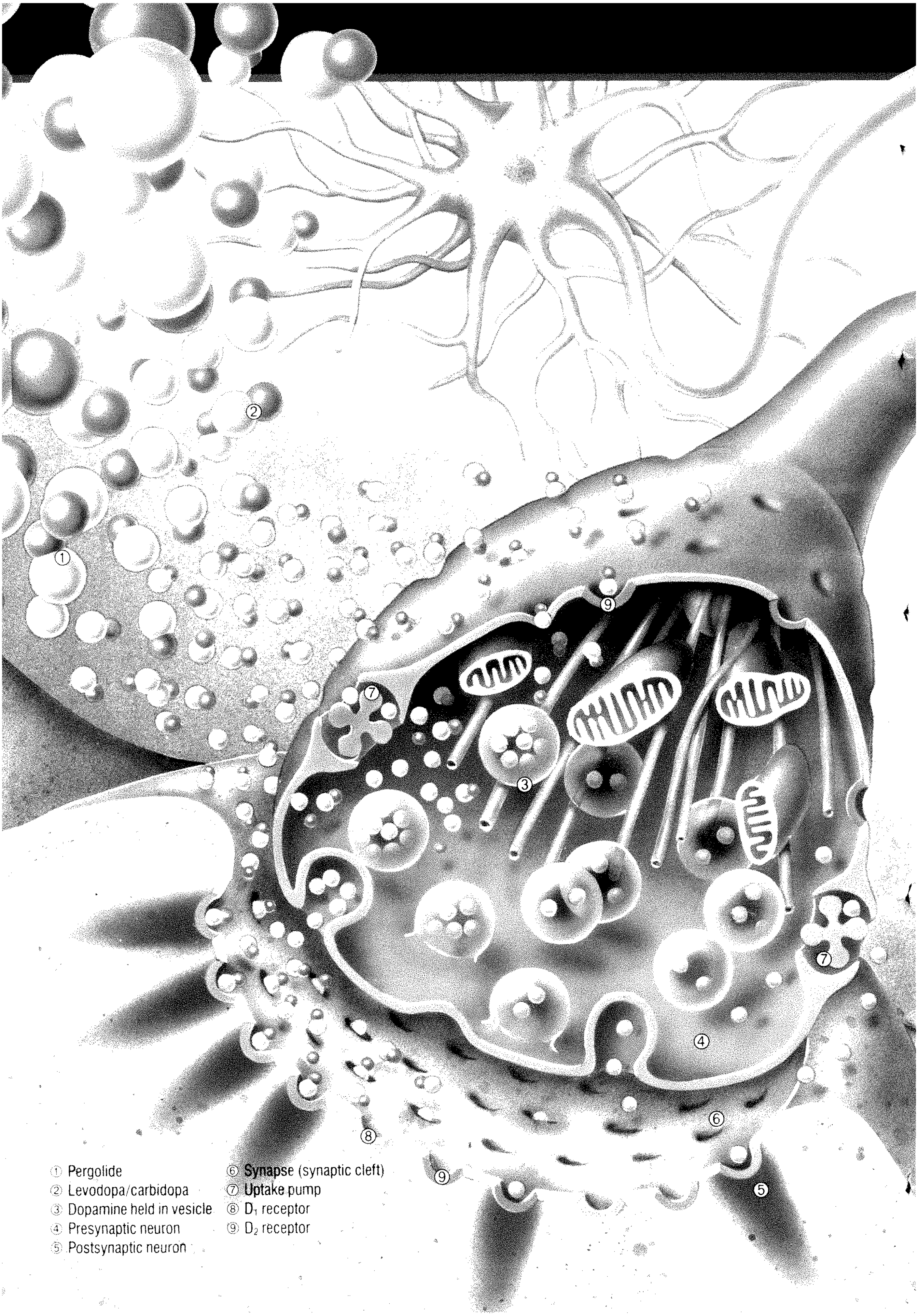
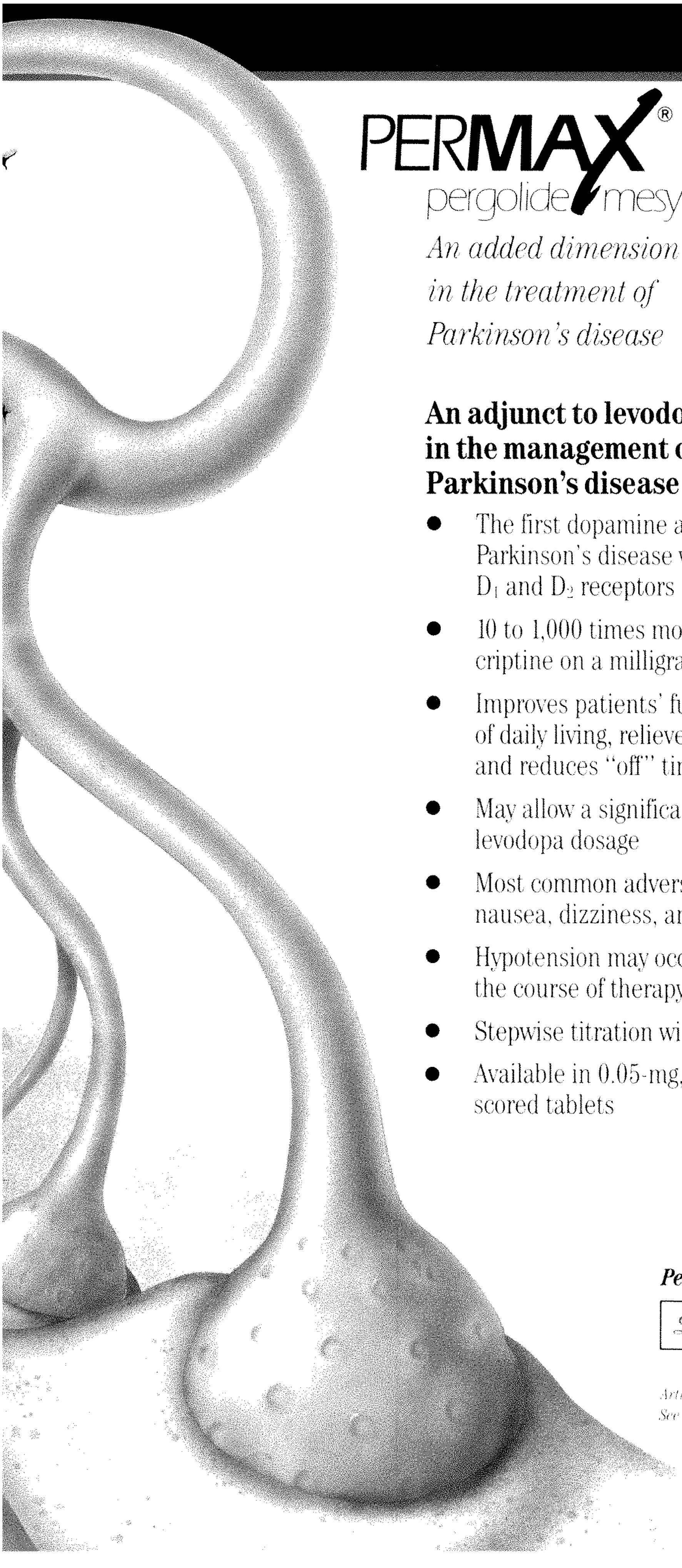


① Pergolide
② Levodopa/carbidopa
③ Dopamine held in vesicle
④ Presynaptic neuron
⑤ Postsynaptic neuron
⑥ **Synapse** (synaptic cleft)
⑦ **Uptake** pump
⑧ D_1 receptor
⑨ D_2 receptor



PERMAX®
pergolide mesylate

An added dimension
in the treatment of
Parkinson's disease

An adjunct to levodopa/carbidopa in the management of patients with Parkinson's disease

- The first dopamine agonist indicated for Parkinson's disease with activity at both D_1 and D_2 receptors
- 10 to 1,000 times more potent than bromocriptine on a milligram-per-milligram basis
- Improves patients' functioning in activities of daily living, relieves signs and symptoms, and reduces "off" time
- May allow a significant reduction in levodopa dosage
- Most common adverse events were dyskinesia, nausea, dizziness, and hallucinations
- Hypotension may occur, especially early in the course of therapy
- Stepwise titration without regard to meals
- Available in 0.05-mg, 0.25-mg, and 1-mg scored tablets

Permax performs

Lilly

Artist's conception of dopamine agonism in the synapse
See adjacent page for prescribing information

Permax*

pergolide mesylate

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to levodopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the sample of patients evaluated had been on levodopa/carbidopa for 3.9 years (range, two days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of levodopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension*—In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis—In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities—In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General*—Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients—Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests—No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions—Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility—A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B—Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers—It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use—Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed*—In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment—Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities—*See* Warnings.

Incidence in Controlled Clinical Trials—The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Events	
Body System/ Adverse Event*	Pergolide Mesylate N=189	Placebo N=187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.[illegible]
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax—This section reports event frequencies evaluated as of October 1988 for adverse events ocurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole—*Frequent:* headache, asthenia, accidental injury, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System—*Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System—*Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System—*Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System—*Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System—*Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System—*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System—*Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusion, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System—*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System—*Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System—*Frequent:* diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System—*Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

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A Comparison of Daily and Alternate-Day Prednisone Therapy in the Treatment of Duchenne Muscular Dystrophy

Gerald M. Fenichel, MD; Jerry R. Mendell, MD; Richard T. Moxley III, MD; Robert C. Griggs, MD; Michael H. Brooke, MD; J. Phillip Miller; Alan Pestronk, MD; Jenny Robison, MS; Wendy King, LPT; Linda Signore, RN, MS; Shree Pandya, MS; Julaine Florence, MS; Janine Schierbecker, PT; Bradley Wilson

• We previously reported the results of a randomized, double-blind 6-month trial of prednisone therapy in which 102 boys aged 5 to 15 years with Duchenne muscular dystrophy received daily doses of 1.5 and 0.75 mg/kg per day and were compared with those receiving placebo. The strength and function in both prednisone-treated groups improved equally and were significantly better than in the placebo group. To compare alternate-day and daily dosing of prednisone with respect to benefits and adverse side effects, the placebo group was started on alternate-day prednisone therapy, and the treatment group regimens were changed to equivalent doses of alternate-day prednisone without breaking the double-blind nature. At the end of 6 months, the group that was changed from daily to alternate-day therapy had declined in strength back to levels observed 12 months previously, at the start of daily therapy. The group in which alternate-day therapy was started showed a significant improvement in strength at 3 months, similar in magnitude to the response of boys treated with daily therapy. However, their strength declined significantly in the subsequent 3 months compared with boys who received daily therapy. The frequency of side effects was not significantly different for alternate-day therapy compared with daily therapy. We conclude that alternate-day prednisone therapy effectively increases strength but does not sustain the improvement to the same extent as daily therapy or mitigate side effects.

(*Arch Neurol.* 1991;48:575-579)

Duchenne muscular dystrophy (DMD), a progressive and fatal disease of skeletal muscle, is a genetic disorder caused by abnormalities at the Xp21 chromosomal site.[1] Affected boys have a complete absence or a reduced or altered size of the structural protein dystrophin in skeletal muscle.[2] The mechanism by which abnormalities of this structural protein produces a clinical syndrome characterized by apparent normal strength at birth and a subsequent progressive muscle deterioration in childhood is not established.[3]

Despite this limited understanding of the pathophysiology, progress has occurred in the development of a treatment. We reported the results of a 6-month randomized, double-blind trial comparing the effects of prednisone (0.75 and 1.5 mg/kg per day) with placebo.[4] Both doses of prednisone significantly improved muscle strength and function compared with placebo. Increased strength was noted as soon as 1 month after the onset of treatment. Strength continued to increase at 3 months and was maintained at 6 months. Both doses of prednisone produced an equivalent response.

In the present study, we sought to compare alternate-day and daily dosing of prednisone with respect to benefits and adverse side effects. Three questions were addressed: (1) Does starting with alternate-day therapy produce the same increase in strength as starting with daily therapy? (2) Can alternate-day prednisone therapy maintain the strength gained after 6 months of daily therapy? (3) Does alternate-day therapy produce fewer adverse side effects than daily therapy?

PATIENTS AND METHODS

A total of 103 boys, aged 5 to 15 years, with DMD were enrolled at the four collaborating institutions for the initial 6-month randomized, double-blind trial of prednisone therapy. Thirty-six were randomized to receive placebo, 33 to receive low-dose prednisone (0.75 mg/kg per day), and 34 to receive high-dose prednisone (1.5 mg/kg per day). Five boys dropped out during the first 6-month study.

Blinding was maintained after the completion of the initial study. In 34 boys who had been receiving placebo, therapy with 2.5 mg/kg of prednisone was started on alternate days. Thirty-one boys were changed from 0.75 mg/kg of prednisone per day to 1.25 mg/kg of prednisone on alternate days, and 33 boys were changed from 1.5 mg/kg per day (maximum, 40 mg) to 2.5 mg/kg of prednisone on alternate days (maximum, 80 mg). Doses were rounded to the nearest 5 mg. Gelatin capsules (No. 3, Eli Lilly & Co, Indianapolis, Ind) containing powdered prednisone were prepared and dispensed from a single pharmacy at The University of Rochester (NY) Medical Center. The capsules included the appropriate milligram-per-kilogram dose plus enough lactose to adjust the final weight to 240 mg. A 6-month supply was dispensed at the onset of the study. One capsule was taken on alternate days at break-

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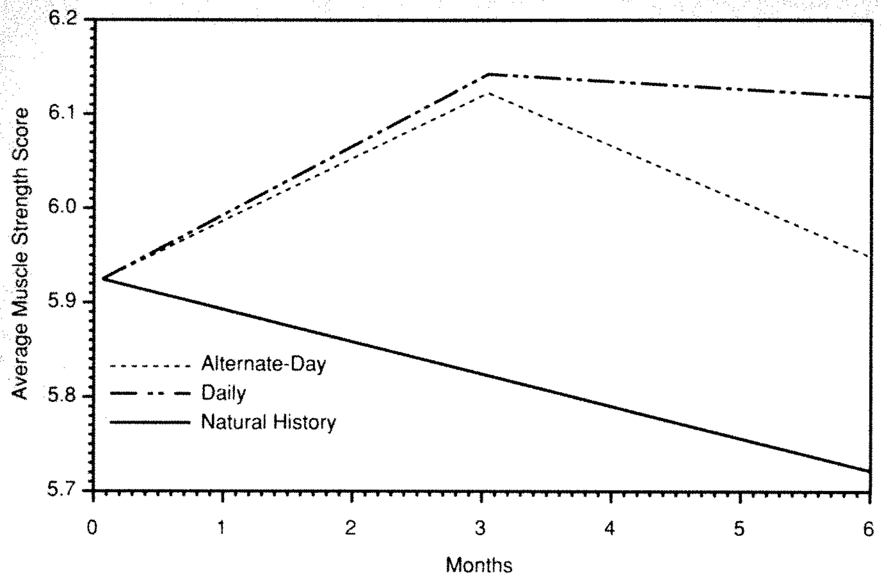

Fig 1.—Graph of least-square means for average muscle strength scores of the group treated with daily prednisone and the group treated with alternate-day prednisone during their initial 6 months of treatment.

fast, and compliance was assessed by weighing the bottles at the time of dispensing and at each return visit.

Two boys dropped out during the present study because of side effects. The number of boys finishing the study were 33 in the group changed from placebo to high-dose alternate-day prednisone, 31 in the low-dose group changed from daily to alternate-day therapy, and 32 in the high-dose group changed from daily to alternate-day therapy.

Clinical Evaluations

All patients were admitted to a Clinical Research Center (CRC) at each collaborating institution at the beginning and at the end of the study. During each CRC admission and on consecutive days, the boys underwent two evaluations of muscle strength, contractures, timed functions, functional grade, lifting of weights, and pulmonary function.[5,6] Clinical evaluations were performed and recorded by Clinical Evaluators who did not inquire about side effects.

Outpatient visits occurred at 1, 2, and 3 months. Clinical evaluations were repeated only at the 3-month outpatient visit. Side effects were evaluated at each outpatient visit and at the CRC admissions by the Principal Investigator without the Clinical Evaluator present. Side effect evaluations included measurement of height, weight, and blood pressure; dip stick measurement of urinary glucose level; and evaluation of behavioral changes, physical stigmas of Cushing's syndrome, cataracts, acne, easy bruising, gastrointestinal symptoms, and hirsutism. Throughout the 12 months of the initial study and the present study, all boys continued to receive calcium carbonate (0.3 g with each meal) and a diet containing 4 g or less of sodium.

Statistical Methods

The relative benefit of starting treatment with alternate-day or daily therapy was made by comparing the measurements made in the placebo group beginning when they changed to alternate-day therapy (second 6 months) with the measurements made when the group treated with 1.5 mg/kg of prednisone first started to receive therapy during the initial study (first 6 months). The mean of measurements at the beginning of the second 6 months was used as the baseline covariate for the placebo group that started to receive alternate-day therapy and those at the beginning of the first 6 months for the prednisone-treated groups. Least-square means were then computed for measurements obtained after 3 and 6 months of therapy. All covariance analyses were computed with Proc GLM of SAS, and type III sums of squares were utilized.[7,8]

The side effects were analyzed with a categorical model with Proc CATMOD in SAS. For the analysis of weight change, a cumulative logit was used as the dependent variable. For the other side effects, the default logit response was used, and paired *t* tests were used to analyze change over time.

The following methods were used to compare the effects of changing from daily therapy to alternate-day therapy. During the CRC admission at the beginning of the study, baseline values were obtained by computing means for each individual measure. Statistical comparisons between high- and low-dose treatment groups at 6, 9, and 12 months were evaluated with use of an analysis of covariance, with each treatment group as the classification variable and the corresponding baseline value for that measure as a covariate. Based on our previous natural history experience, natural log transforms of certain values were utilized when necessary to control for heteroscedasticity. Average muscle strength was chosen a priori as the primary efficacy measure. Least-square means, which adjust the treatment group means for differences in baseline values, were computed for all analyses comparing high- and low-dose prednisone.

Table 1.—Comparison of Daily vs Alternate-Day Prednisone Therapy After 3 Months*

	Least-Square Means		
Measure	Alternate-Day	Daily	*P*
Average muscle strength score	6.14 (0.062) [34]	6.15 (0.069) [30]	.86
Weight lifted, kg	1.49 (0.099) [26]	1.85 (0.094) [29]	.012
Leg function	3.88 (0.119) [33]	3.48 (0.139) [33]	.0497
Time to go 30 ft, s/log (go 30 ft)	8.50/2.14 (0.068) [23]	7.85/2.06 (0.060) [30]	.42
Time to stand, s/log (stand)	5.05/1.62 (0.056) [15]	4.31/1.46 (0.054) [16]	.055
Time to climb stairs, s/log (climb)	4.95/1.60 (0.071) [16]	4.48/1.50 (0.057) [24]	.29
FVC, L	1.60 (0.032) [34]	1.67 (0.035) [28]	.13
MVV, L	41.30 (1.35) [32]	43.90 (1.47) [27]	.21
Systolic BP, mm Hg	106.05 (1.86) [29]	108.15 (1.80) [31]	.42
Diastolic BP, mm Hg	69.40 (1.50) [29]	71.53 (1.45) [31]	.31

*FVC indicates forced vital capacity; MVV, maximum voluntary ventilation; and BP, blood pressure. Values in parentheses are SEs and values in brackets are numbers of subjects.

Paired *t* tests were used to analyze change from the original baseline and from the beginning to the end of the alternate-day therapy period. Single-group *t* tests were used to compare changes in strength scores against natural history trends.[9]

Analyses were performed to compare the side effects experienced by the combined low- and high-dose groups at the 3- and 6-month visits (daily therapy) with the 9- and 12-month visits. For all side effects except weight gain, these matched records were analyzed for change with use of McNemar's test for homogeneity of proportions for correlated samples. For weight gain, a paired *t* test was used to compare the average weight gain for the first 6 months with the average weight gain for the second 6 months. All calculations were performed with SAS.

RESULTS

Starting Therapy: Alternate-Day vs Daily

To compare the 6-month results of starting on alternate-day therapy with those of starting on daily therapy, the average muscle strength scores presented in Fig 1 have been adjusted to the same starting point (the daily treat-

Table 2.—Comparison of Daily vs Alternate-Day Prednisone Therapy After 6 Months*

Measure	Least-Square Means Alternate-Day	Daily	*P*
Average muscle strength score	5.96 (0.052) [34]	6.13 (0.055) [30]	.031
Weight lifted, kg	1.60 (0.104) [26]	2.19 (0.099) [29]	.0002
Contracture index, degrees	−2.28 (0.089) [34]	−2.17 (0.090) [33]	.36
Leg function	4.11 (0.192) [33]	3.66 (0.192) [33]	.101
Time to go 30 ft, s/log (go 30 ft)	8.0/2.08 (0.078) [21]	7.39/2.00 (0.065) [30]	.45
Time to stand, s/log (stand)	4.39/1.48 (0.055) [15]	3.71/1.31 (0.053) [16]	.039
Time to climb stairs, s/log (climb)	4.76/1.56 (0.075) [15]	4.01/1.39 (0.057) [24]	.090
FVC, L	1.73 (0.036) [34]	1.72 (0.040) [28]	.87
MVV, L	44.92 (1.44) [33]	44.12 (1.59) [27]	.71
Log CK	7.89 (0.112) [29]	7.82 (0.110) [30]	.66
Creatinine excretion, mmol/d	2.22 (0.038) [33]	2.24 (0.038) [33]	.85
Systolic BP, mm Hg	105.24 (2.3) [23]	109.76 (2.12) [27]	.16
Diastolic BP, mm Hg	67.99 (2.26) [23]	72.78 (2.08) [27]	.13

*FVC indicates forced vital capacity; MVV, maximum voluntary ventilation; CK, creatine kinase; and BP, blood pressure. Values in parentheses are SEs and values in brackets are numbers of subjects.

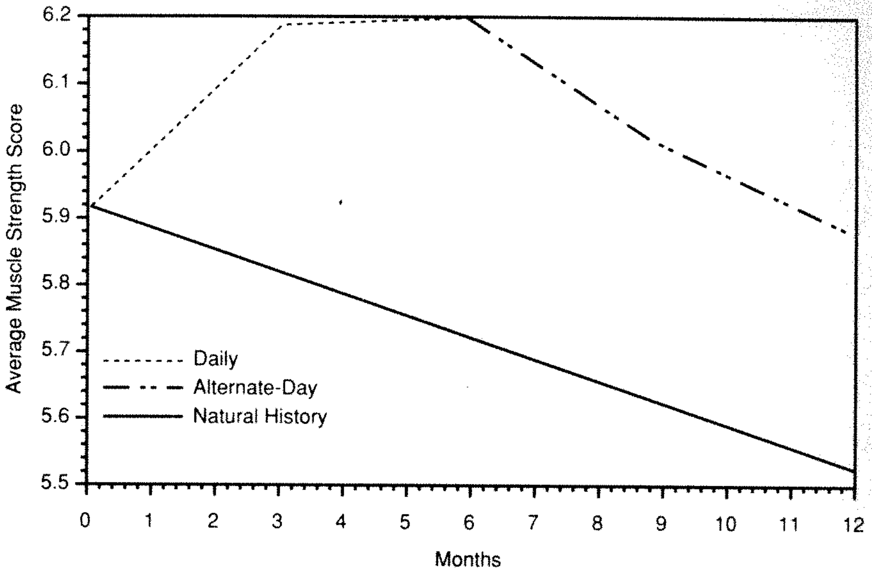

Fig 2.—Graph of average muscle strength scores of boys treated first with daily prednisone (first 6 months) and then with alternate-day prednisone (second 6 months).

Table 3.—Reported Side Effects During the First 6 Months of Therapy With Equivalent Doses of Alternate-Day and Daily Prednisone Therapy*

Side Effect	Alternate-Day (n = 33)	Daily (n = 33)	*P*
Behavioral change	14 (42)	15 (45)	.80
Cataract	0	0	1.00
Hirsutism	12 (36)	17 (55)	.22
Easy bruising	2 (6)	0	.37
Cushingoid appearance	16 (48)	18 (55)	.62
GI symptoms	10 (30)	13 (39)	.44
Rash	7 (21)	9 (27)	.57
Glycosuria	1 (3)	1 (3)	1.00

*Values are number (percent) with side effect. GI indicates gastrointestinal.

Table 4.—Weight Change: Comparison of Daily and Alternate-Day Prednisone Therapy*

% Weight Change	Alternate-Day (n = 34)	Daily (n = 33)
<5	2 (6)	2 (6)
5-10	10 (29)	3 (9)
11-20	13 (38)	17 (52)
>20	9 (26)	11 (33)

**P* = .21. Values are number (percent).

ment group was started 6 months before the alternate-day therapy group). The average muscle strength scores of boys treated with daily and with alternate-day therapy were substantially stronger after 3 months, and there was no significant difference between the two dosing schedules at 3 months ($P = .86$). However, boys treated daily were significantly better than those treated on alternate days in lifting kilogram weights ($P = .012$) (Table 1).

After 6 months, significant differences were noted between alternate-day and daily therapy (Table 2). Muscle strength, as tested by the average muscle strength score and by amount of weight lifted, was maintained on daily therapy but not on alternate-day therapy. After 6 months of alternate-day therapy, the average muscle strength of the group had declined to the level at the start of therapy (Fig 1). However, because there was no net loss of strength during the 6-month trial, they were still substantially stronger than expected from the natural history data.[6] Contracture index, time to go 30 ft, pulmonary function test results, blood pressure, log creatine kinase level, and creatinine excretion did not differ significantly between daily and alternate-day therapy groups (Table 2).

Six months of treatment with either daily or alternate-day prednisone substantially increased the urinary excretion of creatinine. No significant difference was seen between the two treatment groups ($P = .85$).

The number of boys reporting side effects (Table 3) and the percentage of weight gain (Table 4) were not found to be significantly different in a comparison of 6 months of alternate-day therapy with 6 months of daily therapy.

Changing From Daily to Alternate-Day Therapy

The measurements of efficacy and side effects in the daily low-dose and high-dose (0.75 and 1.5 mg/kg per day) groups and in the alternate-day low-dose and high-dose (1.25 and 2.5 mg/kg per day) groups were not significantly different and have been pooled for clarity of presentation.

Alternate-day prednisone therapy did not further improve or even maintain the increased strength achieved with daily prednisone therapy (Fig 2). At the end of 12 months, the average muscle strength scores were almost the same as they had been before daily therapy was started. The average change during the 12-month period of study was −0.01 units. This, however, was significantly better than the natural history trend of −0.38 units per year that we have reported previously ($P = .0001$).[6]

The time required to go 30 ft, to stand up from a lying position, and to climb

Table 5.—Clinical Measures: Changing From Daily to Alternate-Day Prednisone Therapy*

		Daily		Alternate-Day		Paired *t* Test *P* Values		
Measurement	Baseline	3 mo	6 mo	9 mo	12 mo	Baseline vs 6 mo	Baseline vs 12 mo	6 mo vs 12 mo
Average muscle strength score	5.90 ± 1.06 (64)	6.19 ± 1.06 (59)	6.20 ± 1.04 (60)	6.02 ± 1.12 (60)	5.89 ± 1.20 (59)	.0001	.873	.0001
Weight lifted, kg	1.06 ± 0.53 (57)	1.64 ± 0.90 (55)	1.96 ± 1.02 (55)	1.95 ± 0.89 (53)	1.94 ± 0.97 (51)	.0001	.0001	.30
Contracture index, degrees	−2.41 ± 0.92 (64)	−1.72 ± 0.49 (10)	−2.36 ± 1.00 (64)	−1.85 ± 0.66 (16)	−2.36 ± 1.05 (63)	.066	.34	.77
Leg function	3.40 ± 2.84 (64)	3.02 ± 2.81 (63)	3.15 ± 2.91 (64)	3.38 ± 3.00 (64)	3.50 ± 3.08 (61)	.20	.18	.022
Time to go 30 ft, s†	8.67 ± 0.62 (56)	7.24 ± 0.67 (55)	7.03 ± 0.68 (55)	7.61 ± 0.72 (53)	8.00 ± 0.79 (50)	.0001	.28	.0001
Time to stand, s†	6.75 ± 0.57 (35)	5.81 ± 0.72 (40)	5.37 ± 0.77 (39)	5.21 ± 0.60 (33)	5.58 ± 0.65 (32)	.0001	.013	.0001
Time to climb 4 standard stairs, s†	7.46 ± 0.75 (49)	4.90 ± 0.68 (48)	4.57 ± 0.76 (47)	5.26 ± 0.89 (46)	5.31 ± 0.83 (41)	.0001	.003	.0001
FVC, L	1.43 ± 0.50 (60)	1.52 ± 0.50 (59)	1.63 ± 0.50 (59)	1.60 ± 0.52 (61)	1.63 ± 0.47 (59)	.0001	.0001	.93
MVV, L	36.9 ± 14.10 (59)	40.2 ± 15.30 (59)	43.8 ± 15.40 (58)	42.4 ± 15.80 (59)	43.0 ± 14.00 (59)	.0001	.0001	.80
Creatinine excretion, mmol/d	1.67 (64)	. . .	2.21 (64)	. . .	2.85 (60)	.0001	.0001	.77
Log CK	8.18 ± 0.76 (64)	. . .	7.87 ± 0.86 (60)	. . .	7.83 ± 0.74 (52)	.0001	.0001	.63
Systolic BP, mm Hg	104.3 ± 8.70 (65)	107.2 ± 9.50 (64)	108.9 ± 10.70 (58)	107.2 ± 9.60 (57)	108.0 ± 11.40 (50)	.002	.005	.89
Diastolic BP, mm Hg	68.8 ± 8.60 (65)	71.5 ± 8.90 (64)	71.0 ± 13.0 (58)	71.5 ± 10.30 (57)	71.0 ± 10.90 (49)	.21	.02	.55

*FVC indicates forced vital capacity; MVV, maximum voluntary ventilation; CK, creatine kinase; and BP, blood pressure. Values are mean ± SD (number of subjects).

†Means are in seconds and SDs are in log units.

Table 6.—Side Effects: Changing From Daily to Alternate-Day Prednisone Therapy*

Side Effect	Daily	Alternate-Day	*P*
Behavior change†	25 (40)	21 (33)	.58
Cataracts	0	2 (3)	.50
Easy bruising	0	3 (5)	.25
Cushingoid appearance	25 (40)	34 (54)	.064
GI symptoms	24 (38)	16 (25)	.077
Glycosuria	1 (2)	2 (3)	1.00
Hirsutism	30 (48)	28 (44)	.81
Rash	16 (25)	16 (25)	1.00

*Low-dose and high-dose data are pooled. Values are number (percent). GI indicates gastrointestinal.

†Includes only negative behaviors, such as insomnia, hyperactivity, aggression, and emotional lability.

Table 7.—Weight Change: Changing From Daily to Alternate-Day Prednisone Therapy

Variable	Baseline*	6 mo*	12 mo
Mean (SD) weight, kg	25.56 (0.15)	29.96 (0.15)	31.95 (0.15)
No.	62	62	62
% increase	...	17.2†	6.6‡

*Baseline is at the beginning of daily therapy and 6 months is the time that the dosing was changed to alternate day.

†Percent change from baseline to 6 months.

‡Percent change from 6 months to 12 months ($P = .0001$).

stairs had improved in response to daily therapy but worsened at the end of 6 months of alternate-day therapy, declining toward values observed before daily therapy was initiated. In contrast, the increased level of pulmonary function and urinary creatinine excretion and the decreased level of serum creatine kinase achieved during daily therapy were maintained with alternate-day therapy despite the loss of strength (Table 5).

The proportion of boys exhibiting the typical cushingoid appearance continued to increase from 40% after 6 months to 54% after 12 months. Three boys complained of easy bruising, and two boys developed cataracts during the second 6-month period when they were receiving alternate-day therapy (Table 6). Complaints about gastrointestinal symptoms and behavioral problems decreased. The increase in blood pressure observed during the first 6 months was maintained (Table 5), although the weight gain during the second 6 months was significantly less than that observed during the first 6 months ($P = .0001$) (Table 7).

COMMENT

The present investigation is an extension of our previous 6-month randomized trial that demonstrated a beneficial effect of daily prednisone therapy in boys with DMD.[4] In that study, prednisone both at 0.75 mg/kg per day and at 1.5 mg/kg per day had essentially the same beneficial effects on improving average muscle strength. Further study was indicated to establish whether long-term prednisone therapy could slow the progression of weakness. Before starting long-term therapy, it was important to learn whether alternate-day therapy could provide the same benefits with fewer side effects. Previous studies of other diseases have indicated that alternate-day prednisone treatment is associated with fewer serious side effects than daily treatment while maintaining the desired beneficial effects.[10-12]

Starting Therapy: Alternate-Day vs Daily

Therefore, at the end of the initial double-blind study, we initiated therapy with 2.5 mg/kg on alternate days in the placebo group to compare these boys with the boys who had just completed 6 months of daily prednisone therapy (1.5 mg/kg). To make this comparison, the analyses were statistically adjusted to account for the fact that the patients in whom alternate-day therapy was administered had initially been receiving placebo during the 6-month interval when daily therapy was initiated in the other group. At the time of initial randomization, baseline measurements of strength and function were similar for both groups.[4] However, at the start of the second 6-month study, the average muscle strength scores of the boys already treated for 6 months with daily prednisone were significantly greater than the average muscle strength scores of the boys who had been treated with daily placebo ($P = .0001$). The average muscle strength score of the placebo-treated boys had declined 0.21 ± 0.31 units, as expected from the natural history data.[6]

Therefore, the boys in whom alternate-day prednisone therapy was started were not only weaker than the boys in whom daily prednisone therapy was initiated but they had also been asked about side effects for 6 months before starting prednisone therapy. Despite these limitations in the study design, we believe that the reported analyses of efficacy and side effects of initiating treatment with alternate-day and daily prednisone are informative.

Alternate-day therapy (2.5 mg/kg) led to improvements in muscle strength and function after 3 months that were comparable with the improvements observed in boys receiving daily therapy (1.5 mg/kg). However, the improvements were not maintained at 6 months. Urinary creatinine excretion increased with both alternate-day and daily therapies. These observations suggest that the increase in muscle mass inferred from the rise in creatinine excretion[13,14] does not necessarily correlate with the changes in strength observed in the different groups of patients.

Switching From Daily to Alternate-Day Therapy

In boys who had already experienced a benefit from 6 months of daily prednisone therapy, the regimen was changed to an equivalent dose on alternate days to determine whether the beneficial effects could be maintained while minimizing side effects. Alternate-day doses were selected that approximated the daily dose. Disappointingly, the gains in strength observed after 6 months of daily prednisone therapy were lost during the second 6 months of alternate-day therapy. At the time, we were uncertain whether the loss of benefit was due to the change in dosing or whether it would have occurred with continued daily doses. However, subsequent studies have indicated that daily prednisone therapy has a beneficial effect for 2 years and longer.[15]

Adverse side effects are an important concern when treating children with long-term corticosteroids. The increased reports of cushingoid appearance and cataract during the second 6 months of therapy compared with the first 6 months is probably caused by the total duration of prednisone therapy and not the change from daily to alternate-day therapy. The reduced incidence of gastrointestinal and behavioral symptoms may reflect an increased tolerance for these side effects. Weight gain was reduced when alternate-day therapy was used, but it is likely that the percentage weight gain may be greater during the first 6 months of therapy than the second 6 months without regard to the dosing schedule.

Mechanism of Action

The mechanism by which prednisone produces an increase in strength, function, and muscle mass in boys with DMD has not been addressed herein but has been studied. Muscle biopsy specimens obtained at the conclusion of the first 6 months of treatment in a subset of patients compared placebo with prednisone treatment. Dystrophin analysis failed to reveal any differences between the groups.[16] However, mononuclear cell analysis showed that the prednisone-treated groups had significantly fewer total T cells, cytotoxic/suppressor ($CD8^+$) T cells, and muscle fibers focally invaded by inflammatory cells compared with biopsy specimens from the placebo group.[17] These findings are consistent with the prednisone-induced increase in urinary creatinine excretion, which may represent an increase in muscle mass related to decreased muscle destruction.

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References

1. Koenig M, Hoffman EP, Bertelson CJ, et al. Complete cloning of the Duchenne muscular dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. *Cell.* 1987;50:509-517.
2. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. *Cell.* 1987;51:919-928.
3. Rowland LP. Clinical concepts of Duchenne muscular dystrophy: the impact of molecular genetics. *Brain.* 1988;111:479-495.
4. Mendell JR, Moxley RT, Griggs RC, et al. Randomized double-blind controlled trial of prednisone in Duchenne muscular dystrophy. *N Engl J Med.* 1989;320:1592-1597.
5. Brooke MH, Griggs RC, Mendell JR, et al. Clinical trial in Duchenne dystrophy, I: the design of the protocol. *Muscle Nerve.* 1981;4:186-197.
6. Brooke MH, Fenichel GM, Griggs RC, et al. Clinical investigation in Duchenne dystrophy, II:determination of the 'power' of therapeutic trials based on the natural history. *Muscle Nerve.* 1983;6:91-103.
7. Marascuilo LA, McSweeney M. *Nonparametric and Distribution-Free Methods for the Social Sciences.* Monterey, Calif: Brooks/Cole Publishing Co; 1977:167-169.
8. SAS Institute Inc. *SAS/STAT User's Guide, Release 6.03 Edition.* Cory, NC: SAS Institute Inc; 1988.
9. Mendell JR, Province MA, Moxley RT, et al. Clinical investigation of Duchenne muscular dystrophy: a methodology for therapeutic trials based on natural history controls. *Arch Neurol.* 1987;44:808-811.
10. Harter JG, Reddy WJ, Thorn GW. Studies on an intermittent corticosteroid dosage regimen. *N Engl J Med.* 1963;269:591-596.
11. Fauci AS. Alternate-day corticosteroid therapy. *Am J Med.* 1978;64:729-731.
12. Fauci AS, Dale DC, Balou JE. Glucocorticosteroid therapy: mechanism of action and clinical considerations. *Ann Intern Med.* 1986;84:304-315.
13. Forbes GB, Bruining GJ. Urinary creatinine excretion and lean body mass. *Am J Clin Nutr.* 1976;29:1359-1366.
14. Griggs RC, Forbes GB, Moxley RT, et al. The assessment of muscle mass in progressive neuromuscular disease. *Neurology.* 1983;33:158-165.
15. Fenichel GM, Pestronk FA, Miller JP, et al. Prednisone slows strength decline in Duchenne muscular dystrophy: two-year observation. *Neurology.* 1991;41(suppl 1):166. Abstract 182S.
16. Burrow KL, Coovert D, Klein CJ, et al. Dystrophin analysis following prednisone treatment of Duchenne muscular dystrophy. *Neurology.* 1990;40 (suppl 1):206. Abstract 321P.
17. Kissel JT, Burrow K, Rammohan KW, et al. Mononuclear cell analysis of muscle biopsies in prednisone-treated Duchenne muscular dystrophy. *Neurology.* 1990;40(suppl 1):412. Abstract 1076S.

Vegetative State After Closed-Head Injury

A Traumatic Coma Data Bank Report

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• To elucidate the clinical course of the vegetative state after severe closed-head injury, the Traumatic Coma Data Bank was analyzed for outcome at the time of discharge from the hospital and after follow-up intervals ranging up to 3 years after injury. Of 650 patients with closed-head injury available for analysis, 93 (14%) were discharged in a vegetative state. In comparison with conscious survivors, patients in a vegetative state sustained more severe closed-head injury as reflected by the Glasgow Coma Scale scores and pupillary findings and more frequently had diffuse injury complicated by swelling or shift in midline structures. Of 84 patients in a vegetative state who provided follow-up data, 41% became conscious by 6 months, 52% regained consciousness by 1 year, and 58% recovered consciousness within the 3-year follow-up interval. A logistic regression failed to identify predictors of recovery from the vegetative state.

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The essential feature of the persistent vegetative state (PVS) was characterized by Jennett and Plum[1] as "the absence of any adaptive response to the external environment . . . "(p736). Accordingly, posttraumatic PVS patients are distinguished from other survivors of severe head injury who are capable of making a "consistently understandable response to those around them" either by word or by gesture.[1] Despite the inability to obey commands and no comprehensible speech, patients who survive head injury in a vegetative state (VS) may exhibit eye opening and pursuit eye movements. Few recent studies have focused on the PVS, particularly in relation to head injury. Of 110 PVS patients studied by Higashi and coworkers,[2,3] only 38 had sustained a head injury. These investigators reported a 1 year mortality of 41% overall (26% among the head injured), which increased to 73% over 5 years. Although 10% of these PVS patients partially recovered, only three became communicative.

Jennett and Plum[1] did not specify the minimum duration for posttraumatic VS to be considered persistent. However, serial observations have shown that severely head-injured patients rarely are capable of comprehending simple commands within 1 year if they have not done so by 6 months.[4] Of the patients who eventually obeyed commands by 1 year, Bricolo and coworkers[4] found that 13% had done so after the third month, whereas only 1.5% of the patients began to follow commands after 6 months. Limitations of Bricolo and coworkers' study include the retrospective selection of patients and lack of computed tomographic scan information. In a retrospective study of 134 closed-head injured patients who were in a coma persisting over 30 days, Sazbon and Groswasser[5] found that 72 patients subsequently recovered consciousness (54%), most of them during the second and third month. Of the patients who did not recover consciousness during the study period, approximately two thirds died within the first year. Analysis of acute findings revealed that signs of hypothalamic damage (eg, generalized sweating) and a flaccid motor response most clearly differentiated the recovered from the nonrecovered patients, while epilepsy and hydrocephalus were the late complications that most clearly discriminated the two groups.

Analysis of the International Coma Data Bank of 1373 patients with severe head injury has revealed that 140 were vegetative 1 month after trauma (10%).[6] Fifty-nine of the vegetative patients (42%) regained consciousness within 1 year after the onset of coma, including 14 patients (all younger than 40 years) who became independent. Braakman et al[6] reported that age, pupillary reactivity to light, and the best motor response were the most useful prognostic factors for death or continued VS at various time points. Despite wide variation across the four International Coma Data Bank centers in the percentage of patients who were vegetative at 1 month, the findings uniformly ranged from 1% to 2% by 1 year.

This study was undertaken to (1) evaluate the percentage of severely head-injured patients remaining vegetative at the time of hospital discharge following state of the art neurosurgical treatment at four university trauma centers in the United States; (2) characterize the clinical features of patients

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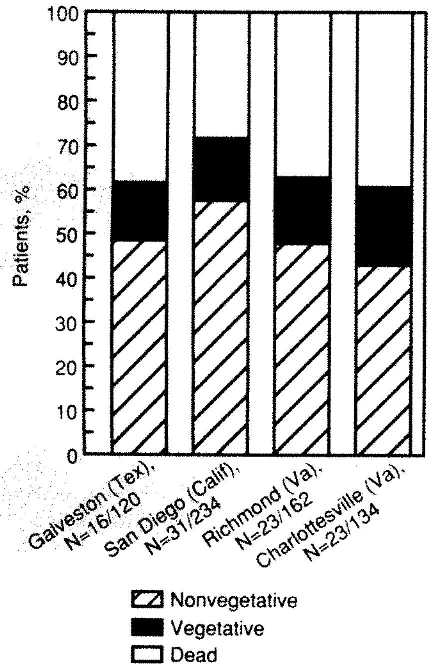

Fig 1.—Distribution of Glasgow Outcome Scale categories at the time of discharge from the Traumatic Coma Data Bank hospitals. The numerator below each bar indicates the number of patients who were discharged in a vegetative state; denominator, the total number of patients discharged from the center.

Table 1.—Age, Duration of Hospitalization, and Intracranial Pressure (ICP) in Vegetative vs Nonvegetative Survivors and Patients Who Were Dead at Hospital Discharge*

	Outcome on Discharge			
	Nonvegetative (n = 335)	Vegetative (n = 93)	Dead (n = 222)	χ^2† (*df* = 2)
Age at injury, y				
Median	25^a	27^b	32^{ab}	31.73
Range	16-84	16-89	16-93	
Hospital stay, days‡				
Median	29^a	59^{ab}	1.5^b	372.95
Range	1-226	5-285	0-242	
Maximum ICP§ in first 72 hours, mm Hg.				
Median	24^a	25^b	41.5^{ab}	102.26
Range	2-93	8-78	4-101	
% Time ICP >20 mm Hg§ in first 72 hours				
Median	4.7^a	9.4^b	41.6^{ab}	113.83
Range	0-91	0-88	0-100	

*A common superscript letter denotes a significant pairwise difference between the groups ($P < .05$) according to a Mann-Whitney test.

†$P < .0001$, Kruskal-Wallis test.

‡Interval from admission to discharge from a Traumatic Coma Data Bank hospital excluding periods in other hospitals.

§Intracranial pressure data available for 305 nonvegetative, 90 vegetative, and 156 dead patients.

discharged in a VS compared with conscious survivors and patients who die while hospitalized; (3) assess the likelihood of recovery from a vegetative condition over the first 3 years after injury; and (4) identify prognostic factors for vegetative patients regaining consciousness.

PATIENTS, MATERIALS, AND METHODS

Patients

Entry criteria for the Traumatic Coma Data Bank[7] (TCDB) included a severe head injury followed within 48 hours by evaluation of the patient in the emergency department at one of the four participating centers (Table 1) as being in a comatose condition as defined by the postresuscitation Glasgow Coma Scale (GCS) of Teasdale and Jennett[8] indicating a score of 8 or less corresponding to no eye opening, inability to obey commands, and absence of comprehensible speech. Patients exhibiting delayed deterioration also were entered into the TCDB, provided that coma ensued within 48 hours of injury. In contrast to the International Coma Databank, there was no stipulation of a 6-hour duration of coma as an eligibility criterion in the TCDB. Of 1030 patients entered into the TCDB, 167 (16.2%) were excluded from this analysis because they sustained gunshot wounds, 121 (14.2%) were deleted because they were brain dead on admission, and 92 (12.4%) were excluded because they were younger than 16 years, leaving 650 patients available for analysis.

Procedures and Schedule of Follow up

The Glasgow Outcome Scale of Jennett and Bond[9] was completed by a neurosurgeon on discharge from the TCDB hospital and at the time of the follow-up examinations that were scheduled at approximately 6 months, 12 months, 2 years, and 3 years after injury. Assessment using the Glasgow Outcome Scale was based on a neurologic examination, interview with the patient, and/or information obtained from the family. The Glasgow Outcome Scale was completed on the basis of a telephone interview with a family member for patients who were unable to return for follow-up. Evaluation of the capacity of patients to execute simple commands (the essential distinction between nonvegetative and vegetative survivors) has been shown to be highly reliable across different clinical examiners.[10]

Analytic Methods

The data were analyzed using χ^2 tests of association, tests for trend, nonparametric methods for comparisons of groups in the absence of normality, survival analyses, and logistic regression.

RESULTS

VS at Discharge

To focus on the comparison between vegetative and conscious survival, the data of patients classified as moderately disabled, severely disabled, or as having made a good recovery were merged into a single category referred to as "nonvegetative." Patients who died were included in the analysis to determine whether their demographic and clinical features more closely resembled the findings in cases of VS as opposed to conscious survivors. This issue is particularly germane to previous studies that have combined the data of patients who died with those who remained vegetative for comparison with conscious survivors.[11,12] Additional analyses were confined to those patients who were vegetative at discharge, and some analyses further excluded those patients who died without recovering from the VS.

Figure 1 shows the distribution of discharge status for each of the four TCDB centers. Overall, 93 of the patients (14%) were discharged from the hospital in a VS. It is seen that the likelihood of this outcome was fairly constant across the four university hospitals. In view of the similar distribution of vegetative survivors across the four TCDB centers and no significant center differences in the distribution of Glasgow Outcome Scale categories at (1) 6 months; (2) 1 year; (3) 2 years; and (4) 3 years; all additional analyses are reported for the total cohort eligible for analysis. Although the initial assessment of outcome was at discharge instead of the 1-month interval employed by Braakman et al,[6] the median length of stay approximated 1 month and three fourths of the patients spent less than 2 months in a TCDB hospital.

Tables 1 through 4 compare the demographic and clinical findings of the 93 patients who were vegetative at the time of discharge from a TCDB center with the corresponding data of nonvegetative survivors and patients who had died. As shown in Table 1, both groups of survivors were significantly younger

Table 2.—Lowest Postresuscitation GCS Score and Pupillary Reactivity in Relation to Outcome at the Time of Discharge From a TCDB Hospital*

	Outcome, No. (%)		
	Nonvegetative	**Vegetative**	**Dead**
GCS score†			
3-5	107 (32)	82 (88)	203 (96.5)
6-15	228 (63)	11 (12)	7 (3.5)
Total	**335** (53)	**93** (15)	**210** (33.0)
	χ^2 (*df* = 2) = 261.1, *P* < .0001		
Pupillary reactivity‡			
Normal	232 (70)	28 (30)	7 (3)
Unilateral abnormality	40 (12)	11 (12)	7 (3)
Bilateral abnormality	61 (18)	54 (58)	199 (93)
Total	**333**	**93**	**213**
	χ^2 (*df* = 4) = 303.26, *P* < .0001		

*GCS indicates Glasgow Coma Scale; TCDB, Traumatic Coma Data Bank.
†Lowest postresuscitation score.
‡Poorest postresuscitation response.

Table 3.—Intracranial Diagnosis Based on CT Scan and Surgery in Relation to Vegetative Outcome at Discharge

	No. (%)			
Intracranial diagnosis	**Nonvegetative***	**Vegetative**	**Dead**	**Total**
Diffuse injury 1, normal	31 (9)	5 (5)	4 (2)	**40** (6)
Diffuse injury 2,†	110 (33)	18 (19)	23 (11)	**151** (24)
Diffuse injury 3,‡ swelling	52 (16)	30 (32)	44 (21)	**126** (20)
Diffuse injury 4,§ with shift	7 (2)	6 (7)	15 (7)	**28** (4)
Evacuated mass lesion	122 (37)	29 (32)	102 (49)	**253** (40)
Nonevacuated mass lesion‖	11 (3)	5 (5)	17 (8)	**33** (5)
Brain-stem injury	1 (3)	0 (. . .)	2 (1)	3 (.5)
Total	**334**	**93**	**207**	**634**

*Computed tomographic (CT) information was unavailable for a single nonvegetative patient.
†Cisterns are present with shift 0 to 55 mm and no high or mixed density lesion of more than 25 mL.
‡Cisterns compressed or absent with shift 0 to 5 mm and no high or mixed density lesion of more than 25 mL.
§Shift of more than 5 mm, no high or mixed density lesion of more than 25 mL.
‖High or mixed density lesion of 25 mL or more not surgically evacuated.

Table 4.—Complications of Injury in Relation to Outcome at Discharge (No. of Patients With Complication/No. of Patients With and Without Complication)*

	No. (%)					
	Nonvegetative	**Vegetative**	**Dead**	**Total**	χ^2	***P***
Shock	66/291 (23)	35/80 (44)	89/189 (48)	**190/560** (34)	36.32	<.0001
Hypoxia	58/189 (31)	18/41 (44)	49/105 (47)	**125/335** (37)	8.24	<.016

*Shock was defined by a drop in systolic blood pressure of less than 90 mm Hg. Hypoxia was defined by a Po_2 of less than 60. These values were recorded in the emergency department at the time of hospital admission. There was variation in the sample size of each group available for analysis because only patients with complications coded as unequivocally present or absent were included.

than the patients who died, whereas the age of vegetative patients did not significantly differ from patients whose consciousness had improved by discharge. Vegetative patients were hospitalized for longer durations at a TCDB center than were conscious survivors (Table 1). It is conceivable that the long duration of hospitalization in the VS patients reflects unavailability of suitable rehabilitation for this group.

Patients who were vegetative at discharge sustained more severe injuries than the conscious survivors, as reflected by their lower postresuscitation GCS scores and more frequent abnormal pupillary reactivity (Table 2). The distribution of GCS scores in the vegetative survivors is similar to the findings obtained in patients who died. However, bilateral pupillary abnormality was more common in fatal injuries compared with the group with vegetative survival, $\chi^2(1)=56.3$, $P<.0001$.

Intracranial diagnosis was characterized using a classification based on the initial computed tomographic scan.[7] In addition, a separate category was designated for patients with brain-stem lesions. In comparison with patients who were following commands at discharge, the intracranial diagnosis of vegetative survivors was distinguished primarily by diffuse injury complicated by swelling or shift of midline structures (Table 3). In contrast, the frequency of mass lesions (total of evacuated and nonevacuated) was similar in vegetative (36%) and nonvegetative (40%) patients, but less common than in patients who died (57%), $\chi^2(1)=19.0$, $P<.0001$.

The presence of shock or hypoxia was analyzed in relation to outcome at hospital discharge for those patients in whom either of these complications was unequivocally present or absent (Table 4). The presence of shock, as defined by a drop in systolic blood pressure to below 90 mm Hg, was more common in patients who died or were vegetative at discharge compared with conscious survivors. Although variation in hypoxia (Po_2, <60) across the groups was less impressive than the disparities in shock, patients who regained relatively normal consciousness by the time of discharge tended to have more normal oxygenation of brain tissue than vegetative survivors or patients who died (Table 4). Intracranial pressure was analyzed according to the maximum value and the percent time it exceeded 20 mm Hg during the first 72 hours of the intensive care phase. Table 1 indicates that intracranial hypertension (reflected by maximum intracranial pressure and the percent time intracranial pressure exceeded 20 mm Hg) was more frequent in the patients who died. Although VS patients tended to have elevated intracranial pressure during a greater percentage of the first 72 hours than patients who were conscious by the time of discharge, this difference was not significant.

Recovery From VS

Of 93 vegetative survivors, outcome data were available for 84 (90%) at least 6 months after injury, whereas nine patients (10%) were unavailable for follow-up. The last follow-up assessment was completed at 6 months in 18 patients (21% of series), 1 year in 35 patients (42% of series), 2 years in 25 patients (30% of series), and 3 years in six patients (7% of series). The demographics and clinical features of patients who recovered from a VS were compared with those who either remained vegetative or died. Table 5 indicates that 49 of the patients discharged in the VS (58%

of the cases with follow-up data) exhibited improvement in level of consciousness within 3 years after injury, whereas 35 of the patients (42%) remained vegetative (n = 15) or died (n = 20) during the follow-up period. Death following discharge in a VS was attributed to medical complications (11 patients), the direct effects of head injury (four patients), or other causes (five patients).

Thirty-four of the vegetative patients (40% of patients with follow-up data) who eventually improved to a higher Glasgow Outcome Scale category had done so by 6 months. Figure 2 depicts the cumulative percentage of vegetative patients who became conscious during the follow-up period. By 1 year after injury, 52% of the VS patients with follow-up data had regained consciousness. As shown in Fig 2, increments in the percentage of vegetative patients who recovered consciousness were slight beyond 1 year, with 49 patients (58% of patients with follow-up data) improved by 2 years. In view of the variable duration of follow-up, Fig 2 should be interpreted as a life-table estimate.

To identify features related to recovery from a VS, the statistical analyses were based on a dichotomy of improved patients vs those who remained vegetative or died during the 2 years. As depicted in Table 5, patients who recovered tended to be younger than survivors who remained vegetative or died, but the difference in age was not significant.

Table 6 shows that the preponderance of patients had a postresuscitation GCS score in the 3 to 5 range irrespective of whether they recovered from a VS at discharge. A repeated analysis confined to the motor component of the GCS also revealed no relationship to recovery from VS. Similarly, nonreactive pupils were common in vegetative survivors regardless of later improvement (Table 6).

The relationship between complications of injury and recovery from PVS is summarized for pulmonary problems, shock, and hypoxia in Table 7. Analysis was confined to unequivocal presence or absence of these complications, excluding "suspected" cases. Of the comparisons between patients who regained consciousness vs those patients who remained in a VS, the only significant finding was an association between absence of hypoxia and PVS (Table 7). Paradoxically, the percent of patients with hypoxia who recovered from PVS was higher than in the patients who remained vegetative. A logistic regression was performed to evaluate the usefulness of patient features in predicting outcome

Table 5.—Outcome of Vegetative State Within 3 Years in Relation to Age at Injury and ICP During First 72 Hours*

	Improved (n = 49)	PVS/Died (n = 35)	PVS (n = 15)	Improved vs PVS/Died Z	Improved vs PVS/Died P	Improved vs PVS Z	Improved vs PVS P
Age, y							
Median	25	28	27	1.56	<0.12	1.04	<.30
Range	16-57	18-74	18-54				
Interval since injury, days†							
Median	376	354	387	...	...	...	...
Range	30-1250	28-1131	33-1132	...	...	...	...
Maximum ICP, mm Hg (n = 43)							
Median	25	24.5	25	.005	<1.0	−0.02	<.98
Range	8-57	12-78	12-78				
% Time ICP, >20 mm Hg (n = 43)							
Median	12.9	5.8	6.7	−1.11	<0.27	−0.66	<0.51
Range	0-75	0-88	0-45				

*Results of the Mann-Whitney test are given by the *Z* score and *P* value. ICP indicates intracranial pressure; PVS, persistent vegetative state.

†Interval until last follow-up evaluation.

Table 6.—Outcome Within the Follow-up Period of Patients Who Were in a Vegetative State at Discharge in Relation to Acute Neurologic Indexes*

	No. (%)		
	Improved (n = 49)	PVS/Dead (n = 35)	PVS (n = 15)
GCS score†			
3-5	42 (86)	33 (94)	14 (93)
6-8	7 (14)	2 (6)	1 (7)
	$P < .29$, Fisher's Exact Test, improved vs PVS/dead		$P < 1.0$, improved vs PVS
Pupillary reactivity‡			
Normal	14 (31)	9 (26)	3 (20)
Unilateral abnormality	7 (14)	3 (8)	1 (7)
Bilateral	27 (55)	23 (66)	11 (73)
	χ^2 (2 *df*) = 1.12, $P < .57$, improved vs PVS/dead		χ^2 (2 *df*) = 1.64, $P < .44$, improved vs PVS

*PVS indicates persistent vegetative state; GCS, Glasgow Coma Scale.

†Lowest postresuscitation score.

‡Poorest postresuscitation response.

Fig 2.—Cumulative percent of vegetative patients regaining consciousness plotted against years after injury for the 84 patients in whom follow-up data were available. Note the small percentage of patients who regained consciousness more than 1 year after injury.

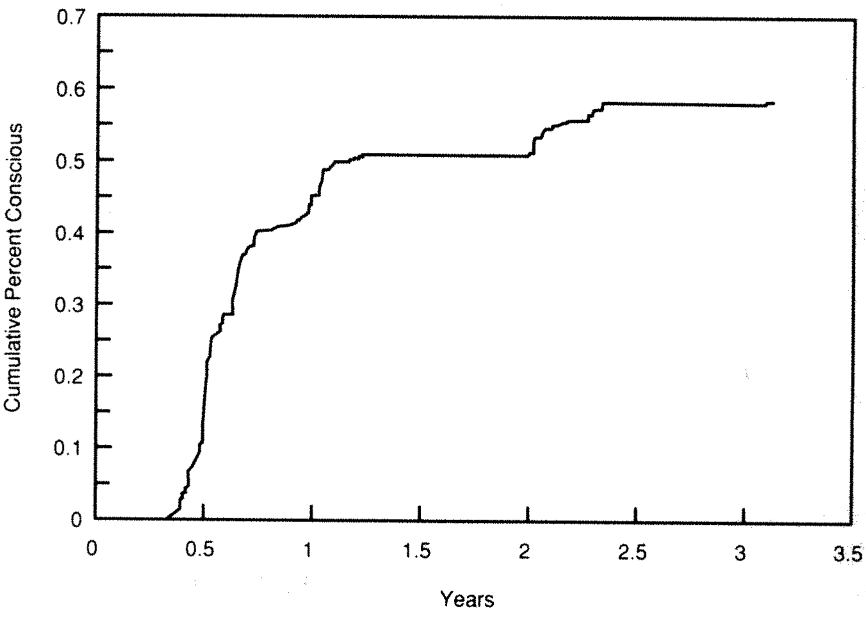

Table 7.—Recovery From a Vegetative State Within 3 Years in Relation to Complications of Injury*

	No. (%)			
	Improved (n = 49)	PVS/Dead (n = 35)	PVS (n = 15)	Total (n = 84)†
Pulmonary problems‡				
None/mild	11 (22)	9 (26)	4 (27)	20 (24)
Moderate/severe	38 (78)	26 (74)	11 (73)	64 (76)
	Fisher's Exact Test, $P < .80$, $P < .74$			
Shock§				
None/mild	40 (82)	26 (74)	12 (80)	66 (79)
Moderate/severe	9 (18)	9 (26)	3 (20)	18 (21)
	Fisher's Exact Test, $P < .43$, $P < 1.00$			
Hypoxia				
Absent	8 (47)	13 (68)	8 (89)	21 (58)
Present	9 (53)	6 (32)	1 (11)	15 (42)
	Fisher's Exact Test, $P < .30$, $P < .01$			

*This analysis was confined to patients in whom the presence or absence of these complications could be unequivocally determined. Patients in whom a complication was suspected were excluded from this analysis. The first probability value refers to the comparison between patients who improved and those who remained vegetative or died, whereas the second probability value refers to the comparison of patients who improved vs those who remained vegetative. PVS indicates persistent vegetative state.

†Of 93 patients discharged in a vegetative state, 83 provided follow-up data.

‡Infection, embolus, insufficiency.

§Clinical rating by neurosurgeon.

Table 8.—Recovery From a Vegetative State Within 3 Years in Relation to Intracranial Diagnosis Based on Initial CT Scan*

	No. (%)		
Intracranial Diagnosis	Vegetative State (n = 15)	Improved Survivors (n = 49)	Dead (n = 20)
Diffuse injury 1, no visible pathologic findings	1 (6.7)	4 (8.2)	0 (0)
Diffuse injury 2	1 (6.7)	10 (20.4)	4 (20.0)
Diffuse injury 3, with swelling	7 (46.7)	16 (32.7)	6 (30.0)
Diffuse injury 4, with shift	2 (13.3)	3 (6.1)	0 (0)
Evacuated mass lesion	3 (20.0)	13 (26.5)	10 (50.0)
Nonevacuated mass lesion	1 (6.7)	3 (6.1)	0 (0)

*Classification of intracranial diagnosis followed previously described guidelines.[7] CT indicates computed tomography.

of VS (ie, improved vs PVS/dead). This analysis disclosed that neither age, pupillary reactivity or swelling on computed tomography were sufficiently predictive of outcome to be selected for entry ($P<.01$) in a regression equation. Further analysis disclosed a nonsignificant trend of more frequent complications in the PVS patients compared with patients who regained consciousness. These findings include posttraumatic hydrocephalus (33% in PVS compared with 24% of improved patients), seizures (13% vs 10%), and inappropriate secretion of antidiuretic hormone (7% vs 4%). Diabetes insipidus occurred in 18% of the patients who improved and in no patient who remained vegetative.

Table 8 shows the distribution of intracranial diagnosis based on the initial computed tomographic scan in the PVS patients, patients who improved, and those who died. It is seen that more than 90% of the PVS patients and patients who regained consciousness had abnormal computed tomographic scans. Diffuse injury with brain swelling was the most common intracranial diagnosis in both groups of survivors. The clearest distinctions seen in Table 8 are the greater observed percentage of uncomplicated diffuse injury among patients who regained consciousness as opposed to the more frequent brain swelling complicating diffuse injury among the PVS patients. Patients who died were distinguished primarily by the higher observed percentage of evacuated mass lesions. There was no significant association between intracranial diagnosis and recovery from a VS.

COMMENT

Despite state-of-the-art neurosurgical management of severe closed-head injury, 14% of the TCDB cohort (excluding gunshot wounds and patients who were brain dead on admission) were discharged from a center hospital in a VS. This proportion of vegetative patients, which was comparable across the four TCDB centers, slightly exceeded the 10% rate of VS obtained from the International Coma Data Bank 1 month after severe injury.[6] In this study, patients discharged in a VS had longer hospital stays than conscious survivors, thus ruling out the possibility that early transfer to a rehabilitation hospital contributed to our findings. In contrast to the International Coma Data Bank,[6] the age of vegetative survivors did not differ from patients who were conscious at the time of discharge from a TCDB hospital, although both groups were younger than hospitalized patients who died from their injuries.

Analysis of the clinical features disclosed that the VS group had lower GCS scores and more frequently exhibited nonreactive pupils than conscious survivors. The severity of impaired consciousness and the frequency of pupillary abnormalities among the vegetative survivors approximated the findings in patients who died before discharge. In contrast, the intracranial pressure values did not differentiate the conscious survivors from the patients discharged in a VS. A review of the intracranial diagnosis, based on the computed tomographic scan and surgical findings, disclosed that diffuse injury associated with brain swelling or shift of midline structures tended to most clearly differentiate the VS patients from conscious survivors. However, even this distinction was limited by considerable overlap (Table 8).

Following discharge in a VS, 52% of the TCDB patients with follow-up data recovered consciousness by 1 year and 58% had improved by the 3-year follow-up interval. Notwithstanding the nine patients (10% of our cohort) for whom follow-up data were unavailable, our findings are in close agreement with a recent study by Sazbon and Groswasser[5] who reported that 54% of closed-head–injured patients eventually regained consciousness after a 1-month duration of "prolonged unawareness," which appeared to be functionally equivalent to VS. Although only 42% of the VS patients in the International Coma Data Bank improved within 1 year after injury,[6] the patient characteristics in this cohort differed from the TCDB patients who were discharged in a VS. Our patients tended to be younger than the posttraumatic VS group studied by Braakman et al.[6] Accordingly, age was prognostic of recovery from VS in the International Coma

Data Bank but not in our cohort. In addition, the TCDB deleted the eligibility requirement of 6 hours of coma that had been used in the International Coma Data Bank.

Taken together with previous longitudinal studies of outcome of posttraumatic VS,[4-6] our findings indicate that recovery from a VS is most likely to occur during the first year as only 6% of the patients followed up improved between the first and second years. Although our data do not exclude the possibility of vegetative patients regaining consciousness after the second year, improvement at such a late stage must be regarded as a rare event.[4,6] In this study, analysis of demographic and neurologic features failed to identify any useful prognostic indicators of recovery from VS. The article by Braakman et al[6] stated that recovery from VS could be predicted by the combination of age and pupillary reactivity to light, and the best motor response received no support from our analysis of the TCDB nor were we able to confirm the prognostic features identified by Sazbon and Groswasser.[5] In contrast to the lack of predictors of recovery from VS, analysis of the TCDB disclosed that the lowest postresuscitation GCS score and pupillary reactivity were predictive of neurobehavioral outcome at 1 year after injury in conscious survivors.[13]

Based on the experience of the TCDB, we postulate that a physiologic measure such as the regional cerebral metabolic rate for glucose and cerebral blood flow may be more useful in predicting the outcome of VS. This possibility is supported by a recent study using positron emission tomography in which cerebral metabolism and cerebral blood flow were markedly lower in vegetative vs locked-in patients.[14]

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The TCDB Manual of Operations that includes the TCDB data forms is available from the National Technical Information Service, US Department of Commerce, 5285 Port Royal Rd, Springfield, VA 22161 (NTIS Accession No. PB87 228060/AS).

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References

1. Jennett B, Plum F. Persistent vegetative state after brain damage. *Lancet*. 1972;1:734-737.
2. Higashi K, Hatano M, Abiko S, et al. Five-year follow-up studies of patients with persistent vegetative state. *J Neurol Neurosurg Psychiatry*. 1981;44:552-554.
3. Higashi K, Sakata Y, Hatano M, et al. Epidemiological studies on patients with a persistent vegetative state. *J Neurol Neurosurg Psychiatry*. 1977;40:876-885.
4. Bricolo A, Turazzi S, Feriotti G. Prolonged posttraumatic unconsciousness. *J Neurosurg*. 1980;52:625-634.
5. Sazbon L, Groswasser Z. Outcome in 134 patients with prolonged posttraumatic unawareness, I: parameters determining late recovery of consciousness. *J Neurosurg*. 1990;72:75-80.
6. Braakman R, Jennett WB, Minderhoud JM. Prognosis of the posttraumatic vegetative state. *Acta Neurochir*. 1988;95:49-52.
7. Eisenberg HM, Gary HE Jr, Aldrich EF, et al. Initial CT scan findings in 753 patients with severe head injury: a report from the NIH Traumatic Coma Data Bank. *J Neurosurg*. 1990;688-698.
8. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. 1974;2:81-84.
9. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. 1975;1:480-487.
10. Teasdale G, Knill-Jones R, Van Der Sande J. Observer variability in assessing impaired consciousness and coma. *J Neurol Neurosurg Psychiatry*. 1978;41:603-610.
11. Jennett B, Teasdale G, Braakman R, Minderhoud J, Heiden J, Kurze T. Prognosis of patients with severe head injury. *Neurosurgery*. 1979;4:283-289.
12. Teasdale G, Skene A, Parker L, et al. Age and outcome of severe head injury. *Acta Neurochir*. 1979;28(suppl):140-143.
13. Levin HS, Gary HE Jr, Eisenberg HM, et al. Neurobehavioral outcome one year after severe head injury: experience of the Traumatic Coma Data Bank. *J Neurosurg*. 1990;73:699-709.
14. Levy DE, Sidtis JJ, Rottenberg DA, et al. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann Neurol*. 1987;22:673-682.

The Influence of Gender on the Susceptibility to Multiple Sclerosis in Sibships

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• A population-based study of pairs of relatives (siblings, second- and third-degree) concordant for multiple sclerosis did not show an excess of like-sexed pairs. In addition, data on human lymphocyte antigen typing for sibling pairs concordant for multiple sclerosis did not find an increase in haplotype sharing for like-sexed pairs. These data do not support the notion that sex-related factors influence multiple-sclerosis susceptibility in families.

(*Arch Neurol.* 1991;48:586-588)

Multiple sclerosis (MS) is one of the most common causes of neurological disability in young adults and is characterized by variable clinical features. In Canada, it has been shown that the prevalence of MS exceeds 1 per 1000 population.[1-3] Although the cause of MS remains unclear, there is increasing evidence that genetic factors play an important, if not essential, role in disease susceptibility.[4,5]

It appears likely that a significant portion of MS susceptibility is polygenic.[6] One susceptibility gene may be linked to histocompatibility antigen (HLA), and others are suspected.[7] Recent evidence suggests that both α and β chains of the T-cell receptor may also be associated with MS, both on a population basis and, for the β chain, in sibling pairs.[8-10] Another susceptibility factor may be sex-related since MS occurs in women approximately twice as often as in men and sex may interact with HLA.[11] In systemic lupus erythematosus where a female-to-male ratio of 10:1 exists, it has been shown that sex and HLA may interact.[12,13]

Weitkamp[14] suggested that the gender of an MS patient may have a modifying role in MS susceptibility by interacting with other factors, such as products of the HLA supergene (the HLA-A3, -B7, -DR2 haplotype is strongly associated with MS[6,15]). Evidence presented by Weitkamp[14] in support of this hypothesis was that relatives (siblings, second- and third-degree) concordant for MS were like-sexed more often than expected by chance.

In the present study, we report observations from two geographically based Canadian MS clinics located in London, Ontario, and Vancouver, British Columbia. The populations of these two regions largely consist of individuals of northern European ancestry, especially from the British Isles. Using data on index cases and their relatives, we attempted to replicate Weitkamp's[14] observations.

PATIENTS, MATERIALS, AND METHODS

The study population consisted of 3046 consecutive, unrelated MS[16] patients attending the clinics in London (N = 1400) and Vancouver (N = 1846). Whenever possible, reportedly affected relatives of patients with index cases were also examined at one of the clinics. If this was impossible, a clinic neurologist reviewed relevant clinical and/or autopsy reports prior to accepting the relative as having MS according to present-day diagnostic criteria.[16]

Data on nine sibships with three siblings having MS and one sibship with five affected siblings were examined separately.

Pairs of relatives were divided into the following three groups: (1) male-male pairs, (2) female-female pairs, and (3) male-female pairs. "Expected" values for the distribution of "like-sexed" or "unlike-sexed" sibling pairs were calculated from the total number of affected male and female subjects in the study population, assuming a random distribution. The data were analyzed for sibling pairs, second-degree relatives (aunt/uncle; niece/nephew; grandparent/grandchild), and first cousins. Parent/child pairs concordant for MS were examined as a separate study population.[17] Data on HLA typing were compiled by combining previously published results.[18,19]

Data on pairs of relatives were analyzed using 2×2 contingency χ^2 analyses. The methodology for HLA typing and the calculation of the expected distribution of haplotype sharing among siblings have been described elsewhere.[18] Differences were considered significant at the 5% ($P<.05$) level.

RESULTS

Sibling Pairs

Comparison of the Distribution of Like-Sexed and Unlike-Sexed Pairs.—A total of 138 concordant sibling pairs (excluding twins and sibships with three or more siblings with MS) were identified from the clinic populations in London (N = 62) and Vancouver (N = 76). There were a total of 83 like-sexed pairs (16 male-male; 67 female-female) and 55 unlike-sexed pairs. The distribution of male-male, female-female, and male-female sibling pairs did not differ significantly between the two clinics ($\chi^2 = 3.95$, df = 2; $P>.05$). Data from both clinics were, therefore, combined for subsequent analyses. As shown in Table 1, the observed number of like-sexed sibling

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pairs was not significantly different than expected ($\chi^2=0.62$, df=1; $P>.05$).

Among the siblings concordant for MS, there were 189 female and 87 male subjects with a female-to-male ratio of 2.1:1. This ratio is similar to the 2:1 ratio observed in the clinic populations.[17]

As seen in Table 1, the nine sibships with three siblings concordant for MS consisted of 14 female and 13 male subjects with a female-to-male ratio of 1.1:1. In one family, there were five siblings with MS (three were female and two were male) with a female-to-male ratio of 1.5:1.

HLA Typing.—Data on HLA typing were available for 48 concordant sibling pairs for whom unequivocal haplotypes were derived[18,19] from the London clinic. As shown in Table 2, the data did not differ from the expected distribution for female-female pairs ($\chi^2=2.43$, df=2; $P>.05$), male-male pairs ($\chi^2=0.33$, df=2; $P>.05$), or female-male pairs ($\chi^2=2.05$, df=2; $P>.05$).

Second-Degree Relative Pairs

From the Vancouver clinic, data were available for 70 pairs of second-degree relatives concordant for MS. As shown in Table 3, the observed number of like-sexed sibling pairs was not significantly different from expected ($\chi^2=0.009$, df=1; $P>.05$). The female-to-male ratio for second-degree relatives concordant for MS was 1.9:1 (92 female and 48 male subjects), not significantly different from the 2:1 ratio for the clinics.[17]

First-Cousin Pairs

From the Vancouver clinic, data were available for 64 pairs of first cousins concordant for MS. As shown in Table 3, the observed number of like-sexed sibling pairs was not significantly different from expected ($\chi^2=2.59$, df=1; $P>.05$). The female-to-male ratio for first cousins concordant for MS was 2.0:1 (85 female and 43 male subjects), not significantly different from the 2:1 ratio for the clinics.[17]

Table 1.—Sex Distribution Among Sibling Pairs Concordant for MS*

	Sibling Pairs			Total No. of Subjects	
Source	**M-M**	**M-F**	**F-F**	**M**	**F**
Sibships With Two Siblings Concordant for MS					
London, Ontario, clinic	10	27	25	**47**	**77**
Vancouver, British Columbia, clinic	6	28	42	**40**	**112**
Total	**16**	**55**	**67**	**87**	**189**
Expected No.†	13.7	59.6	64.7	...	...
Sibships With Three Siblings Concordant for MS					
London, Ontario, clinic	2	2 (2M; 1F)	2	...	...
Vancouver, British Columbia, clinic	...	3 (1M; 2F)	...	...	...
Total	**2**	**5**	**2**	**13**	**14**

*MS indicates multiple sclerosis; M, male; and F, female.

†The expected values represent the binomial distribution predicted from the frequency of each sex, as determined by the total number of M and F.

Table 2.—Haplotype Sharing in Siblings Concordant for MS*

	Sibling Pairs					
	M-M		M-F		F-F	
No. of Shared Haplotypes	**Observed**	**Expected**	**Observed**	**Expected**	**Observed**	**Expected**
2	2	1.5	5	5.25	8	5.25
1	3	3.0	8	10.50	10	10.50
0	1	1.5	8	5.25	3	5.25
Total	**6**	...	**21**	...	**21**	...

*MS indicates multiple sclerosis; M, male; and F, female.

Table 3.—Sex Distribution Among Second-Degree Relative and First-Cousin Pairs Concordant for MS*

	Sibship Pairs			Total No. of Subjects	
Variables	**M-M**	**M-F**	**F-F**	**M**	**F**
Second-Degree Relatives					
Observed No.	8	32	30	48	92
Expected No.†	8.2	31.6	30.2	...	...
First Cousins					
Observed No.	4	35	25	43	85
Expected No.†	7.2	28.6	28.2	...	...

*MS indicates multiple sclerosis; M, male; and F, female.

†The expected values represent the binomial distribution predicted from the frequency of each sex, as determined by the total number of M and F.

COMMENT

It has been proposed by Weitkamp[14] that gender is a risk factor for MS susceptibility, either independent of or interactive with other disease susceptibility genes. If sex is related to disease susceptibility, affected relatives would be more likely to have susceptibility genes identical by descent and the interaction between these genes and sex may be hypothesized to result in a higher proportion of like-sexed concordant relatives than predicted, based on the frequency of male and female subjects in the study population. Weitkamp[14] supported this view by showing that concordant pairs of relatives were more often like-sexed. However, his study is open to criticism as ascertainment was suboptimal and consisted of a literature review for the years 1896 through 1981 inclusive. Publication itself introduces selection biases,[4,20] and the hazards of this type of ascertainment were recognized by Weitkamp. As our study group was identified from two large, population-based MS clinics, ascertainment biases with regard to the sex of affected relatives are minimal. In addition, in the present study, all patients and their relatives were thoroughly assessed and assigned a diagnosis according to standard, recognized criteria,[16] impossible in a literature review. Finally, an excess of concordant, like-sexed sibling pairs does not necessarily imply a genetic mechanism since such pairs may, in fact, have more environmental sharing compared with unlike-sexed siblings.[20] However, it must be noted that unlike-sexed siblings of MS patients still have a significantly greater risk to develop the disease compared with the general population,[5] thus providing more evidence for a possible interaction between genetic susceptibility and environmental sharing.[21,22] Although the data are derived from multiplex sibships, the findings may be equally applicable to both familial and nonfamilial MS, since no differences have yet been found between familial and sporadic cases.[23]

Data from the present study do not support the finding of Weitkamp.[14] An excess of like-sexed pairs was not observed among siblings, second-degree relatives, and first cousins concordant for MS. Our data on parent-child pairs, identified from the same clinic populations and presented elsewhere,[17] are in agreement with those of Weitkamp in that they do not show an excess of like-sexed pairs. In fact, our data show a definite paucity of father-son pairs, whereas the number of mother-daughter, father-daughter, and mother-son pairs occur as expected, based on the female-to-male ratio among MS patients.

Weitkamp[14] also reported an increase in HLA haplotype sharing in female-female sibling pairs concordant for MS. The data on HLA typing presented in this article, an extension of an earlier report,[18] do not substantiate Weitkamp's observations. It is, however, of interest that in lupus erythematosus, a disease with a high preponderance of female patients, male patients show a significant increase in the frequency of HLA-B8 compared with control subjects,[12,13] suggesting that the susceptibility threshold in the relatively resistant male subject is raised by the presence of HLA-B8 DR3. In MS, a sex-related HLA association has been reported (data from London), with female patients having a significantly higher frequency of DR2 compared with male patients and female control subjects.[24]

In general, there is a female sex preponderance among MS patients. In contrast to the data presented by Weitkamp,[14] ours do not indicate a difference in the female-to-male ratio between the general clinic populations and sibships with two affected members, second-degree relatives, or first cousins concordant for MS. Although the numbers are small, a decreased female-to-male ratio (1.1:1) was observed in the nine sibships with three affected members, but the one family with five affected siblings consisted of three female and two male members with a female-to-male ratio of 1.5:1. The influence of the female sex on MS susceptibility may have a parallel in experimental allergic encephalomyelitis, of which the clinical manifestations are limited to juvenile female subjects in the resistant strain-2 guinea pigs.[25] This finding is consistent with the effect of sex on immune responsiveness in this increasingly relevant animal model.

Grufferman and coworkers[22] reviewed the literature on Behçet's disease, Hodgkin's disease, and sarcoidosis and found evidence for increased sex concordance among affected sibling pairs. These data were compared with the findings of Weitkamp.[14] The paucity of concordant conjugal pairs compared with concordant sibling pairs for these four diseases suggests that if shared environmental exposures play a role in family aggregations, these would have to occur during childhood or adolescence.[22] It is possible that gender influences susceptibility on more than one level, as is seen in several animal models of spontaneous autoimmune disease.[26]

In summary, our data do not provide evidence for a relationship between sex and disease susceptibility in relatives concordant for MS.

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References

1. Sweeney VP, Sadovnick AD, Brandejs V. Prevalence of multiple sclerosis in British Columbia. *Can J Neurol Sci.* 1986;13:47-51.
2. Hader WJ. Prevalence of multiple sclerosis in Saskatoon. *Can Med Assoc J.* 1982;127:295-297.
3. Hader WJ, Elliot M, Ebers GC. Epidemiology of multiple sclerosis in London and Middlesex County, Ontario, Canada. *Neurology.* 1988;38:617-621.
4. Ebers GC, Bulman DE, Sadovnick AD, et al. A population-based twin study in multiple sclerosis. *N Engl J Med.* 1986;315:1638-1642.
5. Sadovnick AD, Baird PA, Ward RH. Multiple sclerosis: updated risks for relatives. *Am J Med Genet.* 1988;29:533-541.
6. Ebers GC. Genetic factors in multiple sclerosis. *Neurol Clin.* 1983;1:645-654.
7. Ho HZ, Tiwari JL, Haile RW, et al. HLA-linked and unlinked determinants of multiple sclerosis. *Immunogenetics.* 1982;15:509-517.
8. Matthews WB. Clinical aspects. In: Matthews WB, Acheson ED, Batchelor JR, Weller RO, eds. *McAlpine's Multiple Sclerosis.* New York: Churchill Livingstone Inc; 1985:281-300.
9. Seboun E, Robinson MA, Doolittle TH, et al. A susceptibility locus for multiple sclerosis is linked to the T cell receptor chain complex. *Cell.* 1989;57:1095-1110.
10. Oksenberg JR, Sherritt M, Begovich AB, et al. T-cell receptor V and C alleles associated with multiple sclerosis and myasthenia gravis. *Proc Natl Acad Sci U S A.* 1989;86:988-992.
11. Van Lambalgen R, Sanders EACM, D'Amaro J. Sex distribution, age of onset and HLA profiles in two types of multiple sclerosis: a role for sex hormones and microbial infections in the development of autoimmunity? *J Neurol Sci.* 1986;76:13-21.
12. Bell DA, Rigby R, Stiller CR, et al. HLA antigens in systemic lupus erythematosus: relationship to disease severity, age at onset, and sex. *J Rheumatol.* 1984;11:475-479.
13. Batchelor JR, Welsh KI, Tinoco RM, et al. Hydralazine-induced systemic lupus erythematosus: influence of HLA-DR and sex on susceptibility. *Lancet.* 1980;1:1107-1109.
14. Weitkamp LR. Multiple sclerosis susceptibility: interaction between sex and HLA. *Arch Neurol.* 1983;40:399-401.
15. McDonald WI. The mystery of the origin of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1986;49:113-123.
16. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. In: Poser CM, Paty DW, McDonald WI, Scheinberg L, Ebers GC, eds. *The Diagnosis of Multiple Sclerosis.* New York: Thieme-Stratton Inc; 1984:225-229.
17. Sadovnick AD, Bulman D, Ebers GC. Parent child concordance in multiple sclerosis. *Ann Neurol.* 1991;29:252-255.
18. Ebers GC, Paty DW, Stiller CR, Nelson RF, Seland TP, Larsen B. HLA-typing in multiple sclerosis sibling pairs. *Lancet.* 1982;2:88-90.
19. D'Hooghe MB, Ebers GC. HLA in genetic susceptibility of multiple sclerosis: a recessive effect and the role of other genes. *Neurology.* 1989;39(suppl 1):368.
20. Motulsky AG. Biased ascertainment and the natural history of disease. *N Engl J Med.* 1978;298:1196.
21. Grufferman S, Cole P, Smith PG, et al. Hodgkin's disease in siblings. *N Engl J Med.* 1977;296:248-250.
22. Grufferman S, Barton JW, Eby NL. Increased sex concordance of sibling pairs with Behçet's disease, Hodgkin's disease, multiple sclerosis, and sarcoidosis. *Am J Epidemiol.* 1987;126:365-369.
23. Weinshenker BG, Bulman D, Carriere W, et al. A comparison of sporadic and familial multiple sclerosis. *Neurology.* 1990;40:1354-1358.
24. Charest L, Duquette P. Interaction between sex and HLA in a population study. *Arch Neurol.* 1984;41:703-704.
25. Stone SH, Traugott U, Raine CS. Chronic experimental allergic encephalomyelitis in strain 2 guinea pigs: absence of resistance to nervous system changes and sex dependence of clinical disease. *J Neuroimmunol.* 1983;4:187-189.
26. Smith HR, Steinberg AD. Autoimmunity: a prospective. *Ann Rev Immunol.* 1983;1:175-210.

Incidence and Prevalence of Amyotrophic Lateral Sclerosis in Harris County, Texas, 1985-1988

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• The incidence of amyotrophic lateral sclerosis was determined in Harris County, Texas, for the period 1985 through 1988. Amyotrophic lateral sclerosis cases were ascertained from four sources: area neurologists, hospitals, death certificates, and the Muscular Dystrophy Association. The age-adjusted incidences of 1.27 per 100 000 person-years in males and 1.03 per 100 000 person-years in females were lower than recent rates in the northern US, Canadian, and northern European studies but higher than rates in southern European studies. Comparisons with other recent incidence studies show less uniformity in occurrence of amyotrophic lateral sclerosis, in both the overall rates and in the age- and sex-specific patterns, than was suggested by mortality studies. The incidence of amyotrophic lateral sclerosis among blacks and whites was similar. Hispanic males had incidences similar to white males, although a deficit of female Hispanic cases was found in Harris County. The prevalence of amyotrophic lateral sclerosis peaked in the 65- to 74-year age group at 33 per 100 000 population among males and 19 per 100 000 population for females.

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Amyotrophic lateral sclerosis (ALS) is a progressive disorder of the nervous system that causes degeneration in both upper and lower motor neurons and is characterized by muscular weakness with atrophy, fasciculations, and labioglossopharyngeal paralysis. Amyotrophic lateral sclerosis is uncommon under the age of 40 years, and the incidence progressively increases to at least the age of 70 years, beyond which age most studies show a leveling off or a declining incidence. The clinical course results in death within 5 years from onset in over 80% of cases. For some time, worldwide mortality rates of ALS have shown a strikingly uniform pattern with the exceptions of several foci of extremely high endemicity in the western Pacific. More recent mortality and incidence studies have tended to demonstrate greater population variations and a possible secular increase in occurrence. A trend of increasing ALS death rates has been reported from France,[2] Finland,[3] Scotland,[4] and the United States[5] over the past generation. Morbidity studies in Nova Scotia,[6] Minnesota, Scotland,[4] and Israel[8] have also suggested a secular increase in incidences. However, it is not known to what extent that increase is real or an artifact of more complete case ascertainment.

The purpose of this study was to determine the incidence and prevalence of ALS in Harris County, Texas, for the period 1985 through 1988, and to compare these findings with other populations. This population differs from other populations where the incidence of ALS has been determined in several major ways. Harris County, which includes the city of Houston, is a large urban center with an estimated average population (1985 through 1988) of 2 937 875. The city is multiethnic, with 62% of the total population northern European white, 19% black, and 19% Hispanic. Harris County has been at the heart of the United States petrochemical industry over the last 50 years. Harris County, located on the Gulf Coast, has a subtropical climate, which allows latitudinal comparisons with previous studies.

SUBJECTS AND METHODS

The study population consisted of Harris County residents during the period 1985 through 1988. Cases were ascertained from four sources: (1) Harris County hospitals; (2) neurologists practicing in Harris County and adjacent Galveston County, Texas; (3) the Muscular Dystrophy Association; and (4) death certificates from the Texas Department of Health. Letters were sent to the 149 neurologists who were listed with the Texas Board of Medical Examiners (May 1988) and the 65 hospitals, listed with the Greater Houston Hospital Council, that serve the adult population in the county.

Each hospital contact was asked to generate a computer list of discharges during the study period with the *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICDA-9-CM*) code 335.2. If this was not possible, monthly microfilm and computerized disease indexes were reviewed to obtain the names of patients discharged with the disease code of interest. Of the 65 hospitals contacted, 61 participated. Three of the four nonparticipating hospitals did not have adequate computer capabilities to obtain names by discharge diagnosis, and the other ceased operation in 1988. The nonparticipating hospitals listed the numbers of operational beds as 50, 114, 191, and 320.

Of the 149 Harris and Galveston County neurologists, 101 participated in the study, 32 refused, and 16 had moved out of state or could not be located. Participation was defined as either supplying us with names of cases, stating that no cases of ALS had been seen during the study period, or stating that all cases of ALS were referred to a participating neurologist. Two participating neurologists who specialize in ALS provided extensive computer lists of the patients seen during the study period. Almost half of the nonparticipating neurologists (15 of the 32) practiced in Galveston County. One of these

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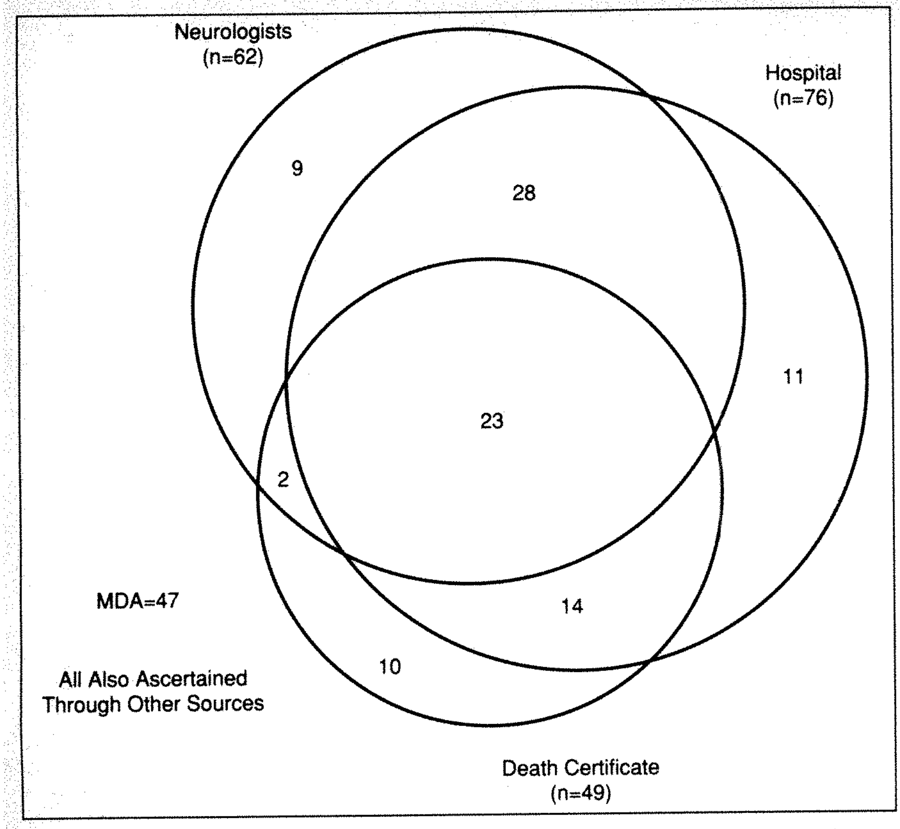
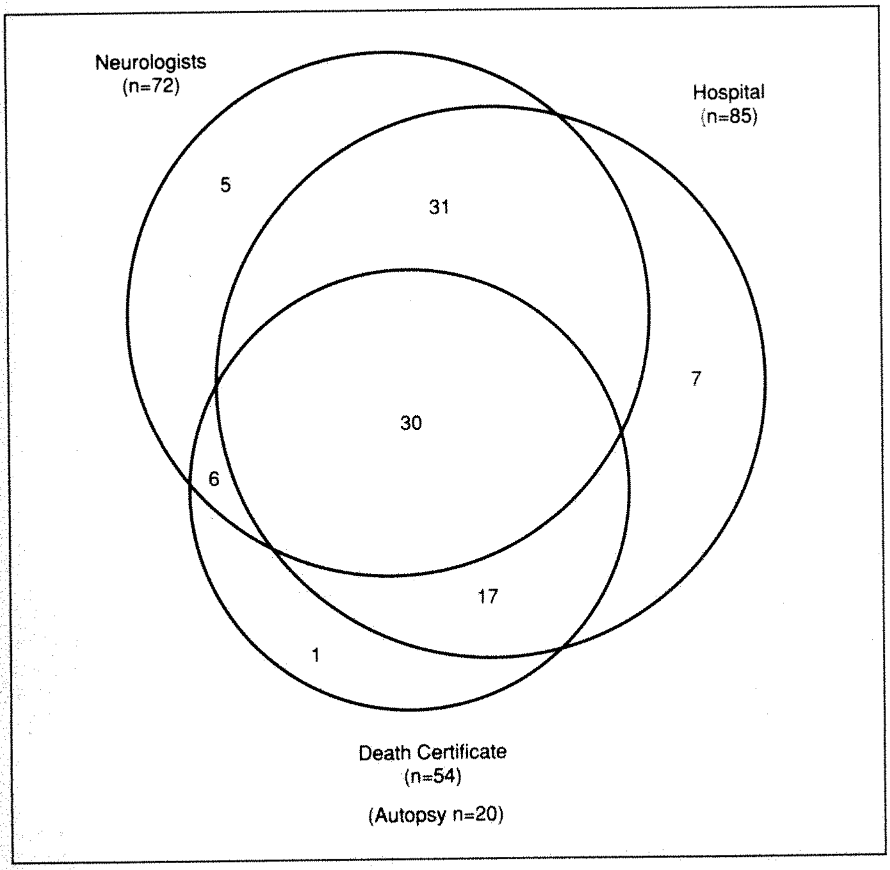


Fig 1.—Amyotrophic lateral sclerosis sources of independent case ascertainment, Harris County, Texas, 1985 through 1988. MDA indicates Muscular Dystrophy Association.

Fig 2.—Amyotrophic lateral sclerosis sources of diagnostic information on 97 incidence cases, Harris County, Texas, 1985 through 1988.



neurologists stated that, to his knowledge, all patients from Harris County with ALS would also have been seen by neurologists in Harris County.

The Muscular Dystrophy Association disseminates information about ALS and assists patients with diagnosis and follow-up care at Muscular Dystrophy Association clinics. Muscular Dystrophy Association records were reviewed for patients with ALS who applied for assistance or were on the current or inactive mailing lists. Patient files were reviewed for the names of the attending neurologists. The neurologists were then contacted for additional information on the case to complete the abstract form and substantiate the diagnosis. Death certificates were obtained from the Texas Department of Health for deaths between January 1985 and December 1989. Search specifications were for certificates with causes of death due to ALS (*ICD-9-CM* 335.2).

Criteria for qualification as an incident case were an initial diagnosis of ALS among Harris County residents between 1985 and 1988. Prevalent cases were of those patients alive and residing in Harris County on January 1, 1989. Addresses were checked with the Houston and Harris County Atlas as well as the Polk Directory and the Southwestern Bell telephone directories when necessary. Clinical information was abstracted from the medical records. Physician diagnosis of ALS was substantiated by patient history and physical examination, electromyogram results, muscle biopsy specimen analysis, death certificate, and autopsy findings. Patients with clinical findings more consistent with other motor neuron diseases, eg, primary lateral sclerosis, progressive muscular atrophy, or polyneuropathy, were excluded. If the diagnosis was uncertain owing to an atypical clinical presentation, coexisting medical conditions, or conflicting diagnoses of two or more neurologists, the completed abstract forms were reviewed by the study neurologist (S.A.) for final determination of case status. Harris County population estimates for each year from 1985 through 1988 were obtained from projections by the Texas Department of Health. The estimates were provided by age, sex, and ethnicity. Age-adjusted rates and age- and sex-adjusted rates were calculated using the 1970 US population as the standard. Ninety-five percent confidence intervals (CIs) were calculated assuming a Poisson distribution.[9] The cumulative risks for Harris County and other populations were computed from the age-specific rates to the age of 80 years using the density method.[10]

RESULTS

A total of 97 incident cases of ALS diagnosed from 1985 through 1988 were identified. Of these, 62 were independently ascertained from neurologists, 76 from hospitals, and 49 through death certificates (Fig 1). The proportion from death certificates was lower than the 80% of patients with ALS who die of ALS because some of the incidence patients were still alive. All 47 of the incidence cases ascertained from the Muscular Dystrophy Association (not shown in Fig 1) were also independently ascertained from at least one other source. Ten cases were independently ascertained solely through death certificates, 11 solely from hospital admissions, and nine solely through neurologists.

After initial ascertainment, additional information from other sources was obtained from hospitalizations, neurology outpatient visits, or death certificates. Figure 2 presents the sources of diagnostic information obtained through all sources. A hospitalization, which usually included an inpatient neurologic examination, was identified for 85 of the patients. An outpatient neurologic evaluation was obtained for 72 cases and a death certificate for 54. Among those who died, autopsy confirmation was obtained on 20. The diagnosis was based solely on death certificate information for one patient, on outpatient neurologic evaluation for five patients, and on hospitalizations for seven.

The crude incidence of ALS for both sexes combined for 1985 through 1988 was 1.10 per 100 000 person-years (95% CI, 0.90 to 1.35), and the age- and sex-adjusted incidence was 1.14 per 100 000 person-years (95% CI, 0.93 to 1.40). The age-adjusted incidence for males was higher than for females, 1.27 per 100 000 person-years (95% CI, 0.95 to 1.69) and 1.03 per 100 000 person-years (95% CI, 0.075 to 1.38), respectively. The age-specific incidence for males reached five per 100 000 person-years in the 55- to 64-year-old age group and remained similar in older age groups (Table 1). In females, the rates peaked in the 65- to 74-year-old age group. Although the rates are low under the age of 45 years, the Harris County rates and proportion of younger cases are higher than those generally reported: 14% of the cases were diagnosed in patients under the age of 45 years. An inspection of these cases did not show a clustering by residency or occupation, and none of these were among the two familial incidence cases. The 14 younger cases were disproportionately black (five cases) compared with whites (eight cases) and Hispanics (one case).

The age-adjusted rates were similar for males in all ethnic groups. The rate was 1.36 per 100 000 person-years (95% CI, 0.96 to 1.87) among white males, 1.10 per 100 000 person-years (95% CI, 0.48 to 2.17) for black males, and 1.27 per 100 000 person-years (95% CI, 0.41 to 2.96) for Hispanic males. For females, the adjusted rates were 1.25 per 100 000 person-years (95% CI, 0.88 to 1.72) among whites, 0.70 per 100 000 person-years (95% CI, 0.28 to 1.44)

Table 1.—Age-Specific Incidence by Gender, Harris County, Texas, 1985-1988

	Male		**Female**		**Total**	
Age, y	**Cases**	**Rate***	**Cases**	**Rate***	**Cases**	**Rate***
15-24	2	0.21	0	0.00	**2**	0.11
25-34	6	0.44	1	0.08	**7**	0.27
35-44	1	0.10	4	0.44	**5**	0.26
45-54	8	1.44	7	1.30	**15**	1.37
55-64	19	5.28	11	2.91	**30**	4.07
65-74	9	5.02	18	7.28	**27**	6.33
≥75	6	5.68	5	2.96	**11**	4.01
Crude	51	1.14	46	1.05	**97**	1.10
Age adjusted†	. . .	1.27	. . .	1.03	. . .	1.15
95% confidence interval		0.95-1.69		0.75-1.38		0.94-1.41

*Rate per 100 000 person-years. Harris County population estimates for 1985-1988 published by Texas Department of Health.

†1970 US total as standard.

Table 2.—Age-Adjusted Incidence by Gender, Comparison With Other Studies

Study	**Rate***	**95% CI†**	**Cumulative Incidence‡**	**Risk‡**
		Male		
Harris County, Texas, 1985-1988	1.27	0.95-1.69	0.0015	1:667
Minnesota, 1925-1984[7]	2.91	1.83-4.40	0.0038	1:263
Middle Finland, 1976-1981[11]	2.04	1.14-3.37	0.0023	1:435
Israel, 1959-1974[8]	0.93	Not computable	0.0011	1:909
Messina, Italy, 1976-1985[12]	0.90	0.61-1.27	0.0010	1:1000
Florence, Italy, 1967-1976[13]	0.68	0.50-0.91	0.0008	1:1250
Ferrara, Italy, 1964-1982[14]	0.62	0.41-2.90	0.0008	1:1250
Mexico, 1962-1969[15]	0.31	0.10-0.72	0.0001	1:8461
		Female		
Harris County, 1985-1988	1.03	0.75-1.38	0.0013	1:769
Minnesota, 1925-1984[7]	1.89	1.18-2.85	0.0025	1:400
Middle Finland, 1976-1981[11]	2.29	1.42-3.51	0.0027	1:370
Israel, 1959-1974[8]	0.56	Not computable	0.0006	1:1666
Messina, 1976-1985[12]	0.22	0.10-0.43	0.0002	1:5000
Florence, 1967-1976[13]	0.47	0.33-0.64	0.0005	1:2000
Ferrara, 1964-1982[14]	0.34	0.20-0.55	0.0004	1:2500
Mexico, 1962-1969[15]	0.46	0.30-0.82	0.0002	1:5709

*Rates per 100 000 person-years, 1970 US total population as standard.

†CT indicates confidence interval.

‡Computed using incidence density method (to age 80 years).

Table 3.—Prevalence by Age and Gender, Harris County, Texas, January 1, 1989

	Male		**Female**		**Total**	
Age, y	**Cases**	**Prevalence***	**Cases**	**Prevalence***	**Cases**	**Prevalence***
15-24	1	0.42	0	0.00	**1**	0.21
25-34	5	1.39	0	0.00	**5**	0.75
35-44	2	0.75	6	2.45	**8**	1.57
45-54	4	2.76	5	3.60	**9**	3.17
55-64	10	10.90	8	8.31	**18**	9.58
65-74	15	32.72	12	18.88	**27**	24.68
≥75	2	7.05	0	0.00	**2**	2.77
Crude	39	3.33	31	2.74	**70**	3.04
Age adjusted†	. . .	3.91	. . .	2.61	. . .	3.12
95% confidence interval		2.78-5.34		1.76-3.70		2.45-3.97

*Prevalence per 100 000 population. Harris County population estimates for 1989 published by Texas Department of Health.

†1970 US total as standard.

among blacks, and only 0.08 per 100 000 person-years (95% CI, 0.002 to 0.46) among Hispanics. The rate for Hispanic females, however, was based on only one case. The numbers of Hispanic and black cases were too small to make meaningful age-specific comparisons.

The cumulative incidence of ALS to the age of 80 years for Harris County in the period 1985 through 1988 was 0.0015 for males and 0.0013 for females (Table 2). Translating this into disease odds, the risk of acquiring ALS to the age of 80 years in Harris County is 1:667 for males and 1:769 for females.

There were 70 prevalent case of ALS in Harris County on January 1, 1989 (Table 3). The overall crude prevalence was 3.04 per 100 000 population (95% CI, 2.39 to 3.86). The crude prevalence for males was 3.33 per 100 000 population (95% CI, 2.37 to 4.53) and for females, 2.74 per 100 000 population (95% CI, 1.86 to 3.89). The age- and sex-specific prevalences presented in Table 3 rise rapidly to the age of 65 to 74 years and then decline among the elderly.

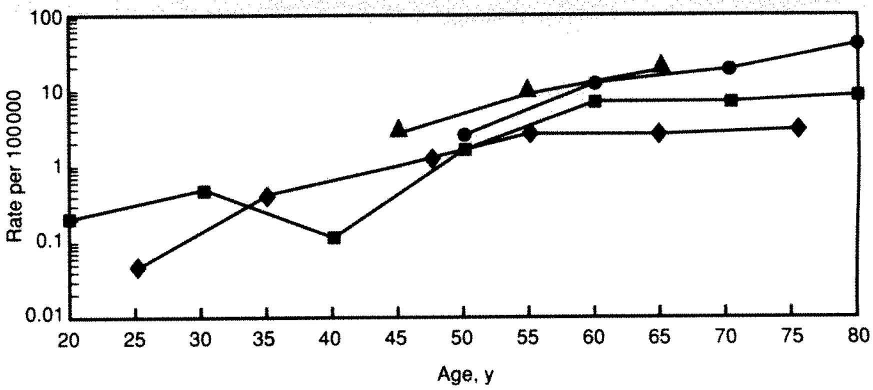


Fig 3.—Amyotrophic lateral sclerosis incidences by age for males in four studies: Harris County, Texas, 1985 through 1988 (squares); Florence, Italy, 1967 through 1976 (diamonds); Rochester, Minn, 1925 through 1984 (circles); and middle Finland, 1976 through 1981 (triangles).

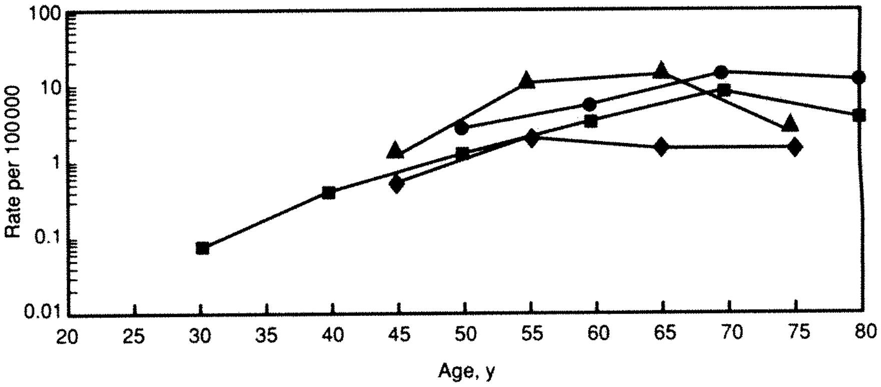


Fig 4.—Amyotrophic lateral sclerosis incidences by age for females in four studies: Harris County, Texas, 1985 through 1988 (squares); Florence, Italy, 1967 through 1976 (diamonds); Rochester, Minn, 1925 through 1984 (circles); and middle Finland, 1976 through 1981 (triangles).

COMMENT

The age-adjusted and cumulative incidence of ALS from worldwide studies, which provided the necessary age- and sex-specific information to adjust to a common standard, are presented in Table 2.[7,8,11-15] The age-adjusted rates in Harris County are intermediate among these, being higher than rates in southern Europe but somewhat lower than those in northern Europe and Rochester, Minn. Although insufficient information is presented in three other recent northern US and Canadian studies, to adjust to a common standard, the crude incidences in these populations (Lehigh, Pa, 1.52[16]; southwestern Ontario, 1.63[17]; and Nova Scotia, 1.95 per 100 000 person-years[6]) are all considerably higher than in Harris County.

The large variation in the frequency of ALS in these studies is illustrated by the odds of ALS developing to the age of 80 years given the reported age- and gender-specific rates and survival to that age. For males, the risk is 1:263 in Rochester, 1:435 in Finland, and 1:667 in Harris County, while risks in Mediterranean populations were on the order of 1:1000. For females, the risks are lower in each population except Finland, where the risk is about 1:400 for both males and females. The age- and sex-specific incidences in Figs 3 and 4 show differing patterns from the northern United States (Rochester), southern United States (Harris County), northern Europe (middle Finland), and southern Europe (Florence, Italy). In males, the Harris County rates are high under the age of 45 years but are considerably lower than Rochester and Finland rates among older men. Unlike most other studies, the Harris County rates in males do not decrease with advancing age but plateau after the age of 55 years. The Rochester rates are unique in that they increase progressively with age. The high incidence in males over 75 years old in Rochester, however, is based on only seven cases. The Harris County rates are higher in all age groups than in Florence and other southern European populations.[12-14] The patterns differ for females in that the rates decline in the oldest age group in all of the studies.

Do these patterns represent real regional differences in the incidence of ALS or do they reflect differences in case ascertainment? It is possible that the low rates from southern Europe are due to the reliance on neurologists as the sole or major source of case ascertainment in contrast to the ascertainment in Rochester, which was based on information from all sources of medical contact. Because of the size of Harris County and the diversity of medical care sources, it is possible that case ascertainment may have been less complete than in Rochester and other higher-latitude North American populations.[16,17] Although there is potentially a greater likelihood of missing cases in Harris County, the extent to which it occurred is presumed to be considerably smaller than the regional differences noted. The four sources of ascertainment employed in this study should have identified patients with ALS who were hospitalized, seen by a neurologist, on the Muscular Dystrophy Association mailing list, or dead through 1989.

If the difference between Rochester and Harris County is due to underascertainment, we would expect the relative deficit of cases in Harris County to be primarily in the older age groups. Elderly cases could be missed because of (1) comorbidity, especially dementia and cerebrovascular disease, which can make the diagnosis of ALS more difficult, (2) less frequent referral to neurologists, and (3) a shorter duration of ALS among older patients. The age-

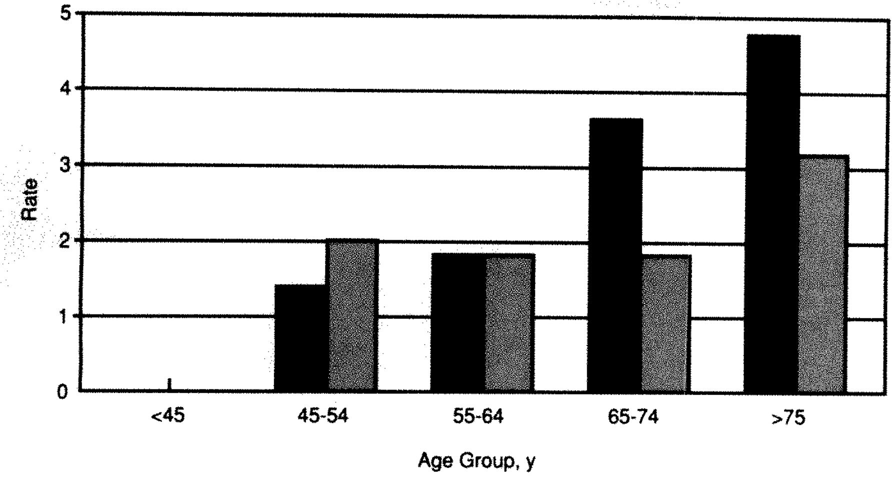


Fig 5.—Amyotrophic lateral sclerosis incidence ratio, Rochester, Minn, vs Harris County, Texas. For age group below 45 years, there were 14 cases in Harris County and none in Rochester. Solid bars indicate males; shaded bars, females. Overall adjusted rate ratios: males, 2.3; females, 1.8; and both, 2.0.

and gender-specific rate ratios between Rochester and Harris County (Fig 5) show the incidences of ALS to be about twice as high in Rochester among females in all age groups rather than confined to the older age groups. The Rochester–Harris County incidence ratio increases with age in males, which is more consistent with less complete ascertainment of cases among older males in Harris County. However, if the difference between Rochester and Harris County were solely due to underascertainment, then half of the 1985 through 1988 Harris County incidence cases in all ages and 45% of those aged 45 though 64 years would have been missed.

Another explanation for the large difference between Rochester and Harris County is that the high rates in Rochester are the chance result of rates based on only 44 cases over a 60-year period. However, this is not supported by an extension of the published Rochester ALS incidence study[7] to the remainder of Olmsted County, Minnesota, for the period 1950 through 1987 and for Rochester from 1985 through 1987, which produces an adjusted rate of 2.1 and maintains the same high rates in a different segment of the Olmsted County population (J.F.A and L. T. Kurland, MD, unpublished data, 1990). In addition, recent Canadian studies report crude rates nearly as high as the Rochester rates in Ontario[17] and higher in Nova Scotia.[6] The pattern of the rates in the United States and Europe suggests a latitudinal gradient in the incidences of ALS. If such a gradient exists, it is not as great as that for multiple sclerosis, but there may be latitudinal differences on the order of twofold. This is one of the few studies to evaluate ethnic differences in the occurrence of ALS. Although mortality studies have shown lower rates in US blacks than whites,[1,5] this difference has not been evaluated in incidence studies. Our results show similar rates in whites and blacks in Harris County. However, since there were only 14 cases among blacks in Harris County, our results do not rule out a modest decrease in blacks compared with whites.

There is some evidence that the incidence of ALS may be unusually low in Mexico. International comparisons show the mortalities in Mexico to be the lowest reported in any country.[1] A study of the incidence of ALS among government employees in Mexico City reported a rate of only 0.4 per 100 000 person-years,[15] which led to the speculation of possible Mexican resistance to ALS. The sex-specific findings of the Hispanic population in Harris County show a deficit in Hispanic females, which is the reverse of that in Mexico City, where the rate was 0.29 for males and 0.50 for females. Therefore, the question of the relative ALS incidence between whites and Hispanics remains unresolved.

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References

1. Kurland LT, Kurtzke JF, Goldberg ID, Choi NW. Amyotrophic lateral sclerosis and other motor neuron diseases. In: Kurland LT, Kurtzke JF, Goldberg ID, eds. *Epidemiology of Neurologic and Sense Organ Disorders.* Cambridge, Mass: Harvard University Press; 1973:108-127.
2. Durrleman S, Alperovitch A. Increasing trend of ALS in France and elsewhere: are the changes real? *Neurology* 1989;39:768-773.
3. Jokelainen M. Amyotrophic lateral sclerosis in Finland. *Adv Exp Med Biol.* 1987;209:341-344.
4. Holloway SM, Emery AEH. The epidemiology of motor neuron disease in Scotland. *Muscle Nerve.* 1982;5:131-133.
5. Lilienfeld DE, Ehland J, Landrigan PJ, et al. Rising mortality from motor neuron disease in the USA, 1962-1984. *Lancet.* 1989;1:710-712.
6. Murray TJ, Cameron J, Heffernan LP, et al. Amyotrophic lateral sclerosis in Nova Scotia. *Adv Exp Med Biol.* 1987;209:345-349.
7. Yoshida S, Mulder DW, Kurland LT, Chu CP, Okazaki H. Follow-up study on amyotrophic lateral sclerosis in Rochester, Minn, 1925 through 1984. *Neuroepidemiology.* 1986;5:61-70.
8. Kahana E, Zilber N. Changes in the incidence of amyotrophic lateral sclerosis in Israel. *Arch Neurol.* 1984;41:157-160.
9. Haenszel E, Loveland DB, Sirken MG. Lung cancer mortality as related to residence and smoking histories. *J Natl Cancer Inst.* 1962;28:1000-1001.
10. Kleinbaum DG, Kupper LL, Morgenstern H. *Epidemiologic Research.* Belmont, Calif: Lifetime Learning Publications; 1982.
11. Murros R, Fogelholm R. Amyotrophic lateral sclerosis in middle-Finland: an epidemiological study. *Acta Neurol Scand.* 1983;67:41-47.
12. DeDomenico P, Malara CE, Marabello L, Puglisi RM, et al. Amyotrophic lateral sclerosis: an epidemiological study in the province of Messina, Italy, 1976-1985. *Neuroepidemiology.* 1988;7:152-158.
13. Bracco L, Antuono P, Amaducci L. Study of epidemiological and etiological factors of amyotrophic lateral sclerosis in the province of Florence, Italy. *Acta Neurol Scand.* 1979;60:112-124.
14. Granieri E, Carreras M, Tola R, et al. Motor neuron disease in the province of Ferrara, Italy, in 1964-1982. *Neurology.* 1988;38:1604-1608.
15. Olivares L, San Esteban E, Alter M. Mexican 'resistance' to amyotrophic lateral sclerosis. *Arch Neurol.* 1972;27:397-402.
16. Zack MM, Levitt LP, Schoenberg B. Motor neuron disease in Lehigh County, Pennsylvania: an epidemiologic study. *J Chronic Dis.* 1977;30:813-818.
17. Hudson AJ, Davenport A, Hader WJ. The incidence of amyotrophic lateral sclerosis in southwestern Ontario, Canada. *Neurology.* 1986;36:1524-1528.

Estimated Prevalence of Dementia Among Elderly Black and White Community Residents

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• A stratified random sample of 83 black and 81 white community residents aged 65 years and older in a five-county area in the Piedmont region of North Carolina was evaluated for dementia, using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, and the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria. Of 164 subjects, 26 were found to be demented, resulting in an estimated prevalence rate of dementia in the five-county area of 16% (95% confidence interval, 7.92 to 24.08) for blacks and 3.05% (95% confidence interval, 0 to 6.91) for whites. The estimated prevalence of dementia for white women (2.9%) was similar to that for white men (3.3%), but the rate for black women was distinctly higher than for black men (19.9% and 8.9%, respectively). Blacks were more likely than whites to have a history of stroke, hypertension, and other chronic disorders that might have contributed to the development of dementia. Apart from differences in rates of institutionalization, no other relevant factors were identified that might explain the difference in the prevalence of dementia in these black and white community residents.

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The comprehensive survey of prevalence studies of dementia presented by Jorm et al in 1987[1] showed that only two of the 47 such epidemiologic studies were concerned with dementia in elderly black populations in the United States. One of these two studies surveyed a rural area of Mississippi and showed that severe dementia was more prevalent among blacks than among whites and among women than among men.[2] The other biracial study was considerably smaller and was conducted within an inner area of Baltimore, Md, surrounding The Johns Hopkins Hospital.[3] The prevalence of dementia was found to be the same in both racial groups, but dementia caused by cerebrovascular disease tended to be more frequent among blacks. Confirmatory evidence of racial differences in the types of dementia was observed at that institution, where 144 patients with clinical diagnoses of dementia were autopsied between 1973 and 1986.[4] Among these, blacks had a significantly higher frequency of multi-infarct dementia and of dementia associated with alcoholism than did whites. White patients, on the other hand, were found to have Alzheimer's disease and Parkinson's disease more often than did blacks.

We describe the estimated prevalence of dementia among black and white elderly community residents in a five-county area in the Piedmont region of North Carolina. A higher prevalence of dementia was found among blacks than among whites, and also among black women than among black men. Cerebrovascular disease also appeared to be considerably more frequent in blacks than in whites, a factor possibly related to the increased frequency of dementia in the former group.

SUBJECTS AND METHODS

Subjects for this study were drawn from the sample members of the Duke Established Populations for Epidemiological Studies of the Elderly (EPESE)[5] project, a longitudinal study of a stratified sample of 4164 community residents aged 65 years and older on whom information is obtained annually.

A four-stage sampling design was used to obtain a probability sample of 4164 persons aged 65 years or older living in households in a five-county region in the Piedmont area of North Carolina. In this geographic area there were 506 census (1980)–defined primary units (eg, blocks, block clusters, and enumeration districts). These primary units varied in population size. Unequal probability replacement sampling, which allows primary units to be selected more than once, was used. The first sampling selection was made from these primary units, and provided 450 zones of equal population size. These zones fell in 332 distinct primary units.

At the second sampling stage one listing unit was selected from each of the 450 zones. At the third stage, the housing units within the selected listing units were listed (n = 26 183), and the expected race (black or nonblack) of each housing unit was recorded. Since by design Duke EPESE intended to oversample blacks (desiring a sample where over 50% would be black), the housing units were stratified by race. All housing units were screened to identify those with elderly residents. Finally, at the fourth stage, the Kish procedure was used to select one elderly person at random from each household in which there were residents aged 65 years and older. Of 5223 subjects selected for the sample, 4164 were successfully interviewed, yielding a response rate of 80%. Of these, 2259 (54%) were black and 1905 (46%) were nonblack. The sampling design permits development of weights, which take into account age, sex, race, geographic location, number of elderly in the household, and nonresponse, so that it is possible to project data from the Duke EPESE sample to the same age population of the five-county area for 1986 and 1987, the baseline year when data were first collected.

Information on selected demographic and health characteristics of this cohort was obtained during the baseline EPESE survey.[5]

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A brief screen of cognitive function, the Short Portable Mental Status Questionnaire (SPMSQ)[6] was also administered at that time. The adjusted score of this measure of cognitive function shows little race or education bias. This testing instrument does not screen for clinical dementia or distinguish between different types of this disorder. It should also be noted that persons appearing to be cognitively impaired on the basis of this instrument are not necessarily demented; however, persons who are demented are expected to be cognitively impaired.

We capitalized on the availability of the SPMSQ scores in the Duke EPESE cohort by drawing a sample that would maximize the likelihood of locating cases of dementia in a manner that would allow the findings to be projected to the five-county older population. To facilitate efficient case finding, the SPMSQ scores were trichotomized, that is, the total EPESE sample was divided into persons with scores below the cutoff for cognitive impairment (in the original standardization sample,[6] scores below the cutoff captured half of the demented subjects), those with one point better than the cutoff, and finally, those with two points better than the cutoff. These three groups were then sorted by race and, within race, by sex and 5-year age group (Figure). Thirty Duke EPESE sample members were dropped, since they were neither black nor white (ie, Hispanic, Asian, and Native American). Eighteen others were also excluded, since their educational level was unknown and their placement on the SPMSQ with respect to cognitive impairment could not be established. The total number of persons represented in our study was, therefore, 4116.

We then selected our subjects from within each of the SPMSQ/race/sex/5-year age groups at random. Within each of the three SPMSQ categories we tried to select the same number of black men as white men, and as many black women as white women, making sure that all 5-year age groups were represented. To obtain the desired 164 subjects (83 black, 81 white), distributed in the relevant categories, 222 persons were contacted. Fifty-eight of these 222 persons declined. Of the 164 subjects who participated in this study, 30% were drawn from the unimpaired SPMSQ group, 38% from those with one point above the cutoff (hereafter called "marginal") score and 32% from those with scores indicating definite cognitive impairment.

A letter was sent to each person selected for the study explaining the nature of the survey. This was followed by a telephone call to arrange for an appointment at the subject's home where interviews were carried out by one of two trained members on our staff. Arrangements were made for each subject and informant to be seen by a neurologist (A.H.) at a locally convenient, nonthreatening site or, failing that, at home. At the initial visit with the respondent, the interviewers collected information for a related study on the sensitivity and specificity of well-established screens for dementia.[7] The results of these tests and those on the initial survey were not made available to the neurologist.

During his examination, the neurologist administered a semistructured interview to each of the 164 subjects. A medical and psychiatric history was obtained, particularly for disorders that might be related to dementia. Specific attention was paid to a history of hypertension, stroke and its sequelae, heart disease, diabetes, cancer, chronic obstructive pulmonary disease, seizures, and other neurologic or metabolic disorders. In addition, questions were asked regarding excess alcohol intake, drug abuse, and cigarette smoking. Information was also obtained on possible serious head injury. The psychiatric history included inquiry into depression and its various possible manifestations and into previous psychiatric disorders and mental retardation. A brief physical and neurologic examination was carried out to assess the general appearance of the subject, the presence of focal motor abnormalities, extrapyramidal signs, gait disorder, myoclonic jerks, and other neurologic dysfunctions. Tests were made for abnormalities in language, motor and constructional praxis, calculation, clock drawing, instrumental and physical activities of daily living, and performance on the SPMSQ screen. The alertness of the subject was assessed. Based on these measures, a diagnosis of dementia and, specifically, of Alzheimer's disease was made, using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*,[8] and the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria.[9] The severity of the dementia, when present, was rated on the Clinical Dementia Rating scale,[10] and factors possibly related to the dementing process (eg, cerebrovascular disease, parkinsonism) were also listed.

RESULTS

Of 164 subjects examined by the neurologist (A.H.), 26 were diagnosed as having dementia (Table 1). This included 19 blacks (seven men and 12 women) and seven whites (three men and four women). Of these 26, 19 came from the group of 53 subjects whose scores were below the SPMSQ cutoff (impaired), four from the 62 whose scores were one point above the SPMSQ cutoff (marginal), and three from the 49 whose scores were two points above the SPMSQ cutoff (unimpaired). The last row of the Figure shows the SPMSQ classes that yielded these 26 demented subjects. As expected, almost all of the demented subjects (23/26) had SPMSQ scores in the definitely or marginally impaired range. The fact that three of those with unimpaired SPMSQ scores were found to have dementia attests to the fact that this screening test may produce false-negative results. It is evident that no precise cutoff point can be used to ensure the detection of all demented cases in a population survey.

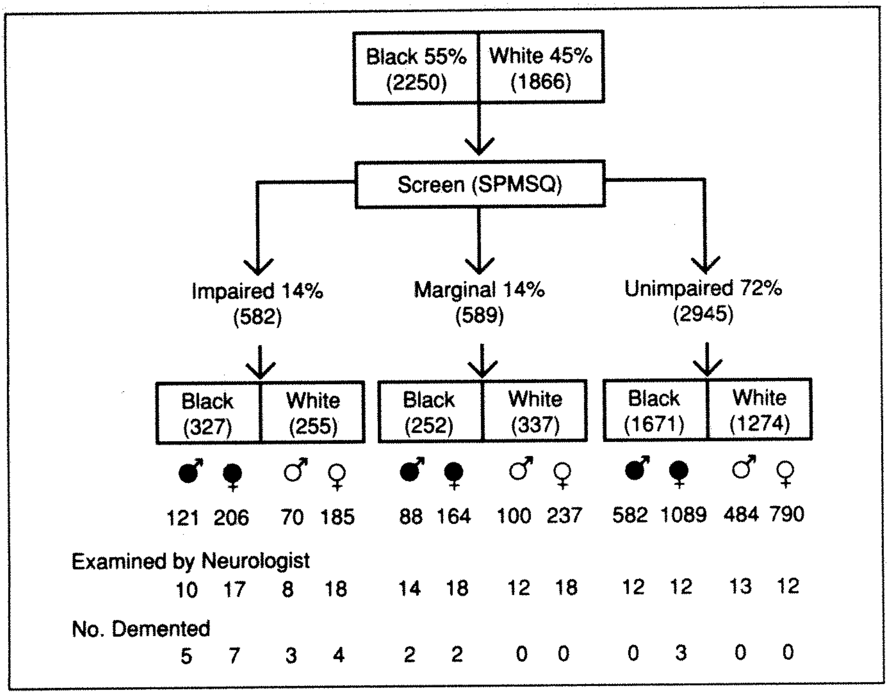
It is also of interest that only seven (26.9%) of the 26 white subjects with impaired SPMSQ scores were found by the neurologist to be demented compared with 12 (44.4%) of 27 blacks with impaired scores in this screening test (see lower two rows in the Figure). This disparity in the diagnosis of dementia in the two racial groups with impaired cognitive function led us to look for various disorders other than dementia that may have been present in the blacks and whites with impaired cognitive function.

Table 1.—Distribution of Demented Subjects

	Black	White
Probable Alzheimer's disease	12	4
Mixed or multi-infarct dementia	5	1
Systemic cancer or brain tumor	2	1
Parkinson's disease	...	1
Total	**19**	**7**

In this regard we reviewed the possibility of three major conditions related to cognitive dysfunction in the elderly: (1) age-associated memory impairment as assessed by the neurologist, and (2) depression, and (3) significant impairment in activities of daily living as assessed by a close friend or family member. The percentages of blacks with cognitive impairment but without dementia who had such disorders were 20.0% for age-associated memory impairment, 26.7% for depression, and 40% for activities of daily living compared with 16.7%, 11.1%, and 55%, respectively, in whites. These data would not support a conjecture that standards for accepting dementia among blacks were more lenient than those for whites.

The medical records for all 26 subjects were requested from their physicians and hospitals. Thirteen (50%) of them were found to have been diagnosed as having dementia by previous hospital or clinic examinations. Of the remaining 13 subjects, seven were referred to the Memory Disorders Clinic of Duke University Medical Center, Durham, NC, for evaluation by a second neurologist (C.C.) experienced in the diagnosis of dementia. There, a complete neurologic examination and a structured neuropsychologic evaluation were carried out along with appropriate laboratory studies and magnetic resonance imaging of the brain. All seven of these subjects were diagnosed as having Alzheimer's disease. Of the remaining six subjects, two died before further evaluation could be carried out, and the remaining four could not travel to the clinic because either they were confined to nursing homes or their dementing disorder was too severe.



Estimating prevalence of dementia in five North Carolina counties. Flow chart shows process for deriving the stratified random sample from the 4116 black (aged 65 years or more) and white (aged 65 years or more) subjects screened for cognitive impairment. SPMSQ indicates Short Portable Mental Status Questionnaire.

Among the 26 demented subjects, seven were classified, on the basis of the Clinical Dementia Rating scale,[10] as having severe dementia, eight as moderate, and 11 as mildly demented. The blacks and whites did not differ significantly in their ability to perform instrumental activities of daily living or personal self-maintenance tasks.

The data obtained from the subjects selected for neurologic examination were weighted to provide estimates of the prevalence rates for dementia in the black and white population aged 65 years and older in the five-county area. The total Duke EPESE sample and the subjects in this study were both classified into 60 mutually exclusive groups on the basis of their SPMSQ scores (impaired, marginal, unimpaired), race, sex, and 5-year age categories (65 to 69 years, 70 to 74 years, 75 to 79 years, 80 to 84 years, and 85 years and more). The weights developed for the total Duke EPESE sample not only took into account initial nonresponse (based on sex, age, and area of residence) but also adjusted for deliberate oversampling of blacks (from 54% in the Duke EPESE sample to 35% in the five-county area). Equivalent sample sizes (that took design effects into account) were calculated for both the Duke EPESE sample and this study. The weighted proportion of demented subjects within each of the groups in this study was then determined. This proportion was then applied to the corresponding weighted Duke EPESE sample group to obtain the estimated number of demented subjects in each of the 60 groups into which the total sample had been classified. Summation across appropriate subgroups yielded estimated numbers, which were then converted into population-relevant percentages, separately for blacks and for whites, and within these groups for men and for women. Age-based prevalence estimation is also feasible, but was not calculated because of the relatively small numbers of demented subjects ascertained in this study.

Table 1 lists the types and likely causes of dementia among the 26 cases. Probable Alzheimer's disease (diagnosis based on the National Institute of Neurological Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria),[9] appears to be the most common cause, representing 16 of 26 cases. Mixed Alzheimer's disease and cerebrovascular disease or multiple strokes alone (multi-infarct dementia) accounts for an additional six demented subjects. Five of these six cases were black and one was white. All six of them had a history of sudden onset of a prior stroke with focal neurologic deficits associated with residual evidence of hemiplegia, aphasia, or other cerebrovascular focal signs. Two other subjects with dementia had a history of systemic cancer, another one had neuroimaging evidence of a large cystic tumor associated with diffuse, severe atrophy of the cerebral cortex. The remaining one of the 26 persons with dementia had a history of early-onset parkinsonism following encephalitis. Definite mental impairment was observed, which could be related to this illness or perhaps to an intracranial surgical operation for relief of the incapacitating extrapyramidal manifestations. In three of 16 persons with probable Alzheimer's disease, a history was obtained of secondary cases of dementia among their first- or second-degree relatives, suggesting the possibility of the familial type of this illness.

Table 2 shows the estimated prevalence rates of dementia weighted to represent the elderly population (aged 65 years or older) in the five-county area. The estimated prevalence rate of dementia was 8.9% for black men, 19.9% for black women, 3.3% for white men, and 2.9% for white women. The overall estimated prevalence rates for blacks and whites were 16% (95% confidence interval, 7.92 to 24.08) and 3.05% (95% confidence interval, 0 to 6.91), respectively. Because of the small sample sizes, the standard errors and confidence intervals are large and interpretation of the data should be cautious, particularly for the marked differences observed in prevalence by gender in the black elderly. It does seem clear, however, that overall, blacks have a much higher prevalence of dementia than do whites ($P<.002$). While the estimated prevalence of dementia is greater among black women than among black men, the difference is not statistically significant ($P<.08$) because of the small sample size. The small sample size also makes calculation of the age-related prevalence of dementia inappropriate.

Table 3 compares the history of vascular disease and diabetes (noted during the 1986 and 1987 baseline survey) among subjects diagnosed as demented with that present in the total EPESE sample of blacks and whites. A history of heart attacks, high blood pressure, diabetes, and stroke was reported more often by blacks with dementia than by whites with this cognitive disorder. The fact that blacks in general (and particularly black women) were much more likely than whites to give a history of hypertension and diabetes suggests that these conditions may be implicated in the higher proportion of vascular dementia (mixed or multi-infarct dementia) noted among the black subjects.

COMMENT

The results of our study confirm those reported by Schoenberg et al[2] who also

Table 2.—Estimated Prevalence of Dementia by Race and Sex

	Percent	
	Black Prevalence (SE)	White Prevalence (SE)
Male	8.93 (4.95)	3.30 (3.20)
Female	19.87 (5.93)	2.91 (2.51)
Total	16.00 (4.12)	3.05 (1.97)

Table 3.—Selected Chronic Diseases by Race, Sex, and Dementia Status

	Percent					
	Black			White		
	All Males (n = 797)	All Females (n = 1463)	Demented (n = 19)	All Males (n = 657)	All Females (n = 1218)	Demented (n = 7)
Heart attack	11.4	10.3	5.3	19.3	11.1	0.0
High blood pressure	47.7	67.0	68.4	40.0	51.6	42.9
Diabetes	17.2	24.3	27.8	13.6	11.8	14.3
Stroke	9.4	8.4	26.3	9.6	5.3	14.3

Table 4.—Refusals by Initial Cognitive Class, Race, and Sex

	Initial Cognitive Class			
	Unimpaired	Marginal	Impaired	N
Black				
Male	6	5	2	**13**
Female	4	3	6	**13**
White				
Male	3	3	5	**11**
Female	9	10	2	**21**
Total	**22**	**21**	**15**	**58**

screened a large southern biracial rural community for dementia. That study, however, examined both household and institutionalized persons and reported only severely demented cases. Both their study and this one found a higher prevalence of dementia among blacks than whites, and among black women compared with black men. On the other hand, the relatively small study of an inner-city biracial community reported by Folstein et al[8] failed to show any significant differences in the frequency of dementia in the two racial groups. That study did, however, show that demented blacks were more likely than whites to have cerebrovascular disease associated with dementia—results similar to our own. We did not confirm their findings, however, that multi-infarct dementia was more common than Alzheimer's disease among blacks. Confirmatory evidence of racial differences in dementia has been reported in studies of death certificates[11] that showed blacks to have a higher reported prevalence of dementia at death than whites, and in an autopsy series[4] (admittedly not a random sample) that found that dementia was twice as prevalent among blacks as among whites.

The differences in the prevalence of dementia between blacks and whites noted in our study are substantial and statistically significant. The question arises whether factors in the design or procedural methods of the study could account for such differences. The risk of drawing major conclusions from the relatively small sample used in this study has been commented on earlier, and the need for confirmatory studies in larger biracial populations is evident. The question also arises as to whether the differences may be related to an earlier age of onset of this disorder or to a less progressive course of the illness among blacks. Unfortunately, the number of cases of dementia in this study are too small to provide such data. There is, moreover, little, if any, information in the literature on the age of onset of dementia among cases of vascular dementia compared with subjects with Alzheimer's disease or those with dementia caused by other diseases. Precise information on the age of onset of the dementing process in any of these groups of cases is difficult to obtain, since it depends largely on the observations of the subject's spouse or other caregivers. Other factors that might account for the differences in the observed prevalence rates are considered below.

The fact that the whites in this community are more likely than blacks to institutionalize their cognitively impaired family relatives may help to explain the lower prevalence rates of dementia among the white noninstitutionalized residents. One- year follow-up of the Duke EPESE sample indicates that there is a higher annual rate of nursing home entry among whites (3.1%) than among blacks (2.1%). With a cap of approximately 5% on nursing home beds in this area, roughly three quarters of the beds are occupied by whites and one quarter by blacks, ie, the 5% can be divided approximately into 3.75% white and 1.25% black residents. National estimates of 50% for the prevalence of dementia among nursing home residents would suggest that 1.8% of these whites and 0.6% of these blacks might be demented. This would not fully explain the lower rate of dementia found among white community residents. So, while the differential rate of institutionalization may modify the black-white difference in dementia prevalence by perhaps 1%, it certainly does not close the gap.

It has been suggested[12] that the level of education (probably as a surrogate for other factors) may relate to the presence of dementia. Blacks in our study have a lower level of education and this, in some way, could be a factor explaining the difference in the prevalence rate of dementia in the two racial groups. On analysis, however, no relationship was found between level of education and the presence of dementia in this cohort.

It has also been suggested that racial differences in survival rates could be implicated in our observations on the estimated prevalence of dementia in this community. In the general US population blacks are known to be at a higher risk for death than whites prior to age 75 years, but the reverse has been observed after this age. A decrease in the death rate among blacks in the older age groups could possibly account for a higher prevalence rate of dementia. However, in the Duke EPESE sample, the age pyramid for blacks is comparable with that for whites. For this group, differential survival does not seem to explain the findings.

It is possible that blacks and whites may have differed in the extent to which they participated in the study. Analysis of refusal rates in this survey (Table 4) showed that there was no major difference in participation between blacks and whites. The cognitively impaired do not appear to have been unduly shielded. Indeed, refusal was lowest for the most cognitively impaired and was particularly low among cognitively impaired white women. Thus, this factor does not appear to be important in explaining the racial differences in prevalence rates for dementia observed in this study.

The prevalence rate of dementia (3.05%) in whites 65 years of age or older in our study is similar to that (3.5%) described by Kokmen et al[13] in the largely white community of Rochester, Minn. That investigation was based on information available in local medical records, but the observed rates are considered by the investigators to be comparable with those obtained by most population surveys. In a recently reported survey of 3623 white East Boston, Mass, community residents aged 65 years and older, however, an unusually high prevalence rate of 10.3% for probable Alzheimer's disease was estimated.[14] However, few of the elderly residents from that location had been institutionalized.

As mentioned above, the fivefold higher rates we observed in the blacks compared with the whites may be related to a history of stroke and hypertension that was present in a significant proportion of the blacks. The extent to which these vascular illnesses contributed to the development of dementia in this racial group cannot be determined without postmortem examination of the brain. As stated earlier, black and white demented subjects did not differ significantly in their ability to perform instrumental or physical activities of daily living, suggesting that comparable objective impairment criteria were indeed used in identifying dementia. Further, all of the subjects diagnosed as having dementia in the field study and for whom additional diagnostic information was available from prior records or subsequent examination by another physician were found to have this disorder. Therefore, there seems little reason to doubt the accuracy of the overall diagnosis of dementia in this group.

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References

1. Jorm AF, Korten AE, Henderson AS. The prevalence of dementia: a quantitative integration of the literature. *Acta Psychiatr Scand.* 1987;76:465-479.

2. Schoenberg BS, Anderson DW, Haerer AV. Severe dementia: prevalence and clinical features in a biracial US population. *Arch Neurol.* 1985;42:740-743.

3. Folstein M, Anthony JC, Parhad I, Duffy B, Gruenberg EM. The meaning of cognitive impairment in the elderly. *J Am Geriatr Soc.* 1985;33:228-235.

4. De la Monte SM, Hutchins GM, Moore GW. Racial differences in the etiology of dementia and frequency of Alzheimer lesions in the brain. *J Natl Med Assoc.* 1989;81:644-652.

5. Cornoni-Huntley J, Blazer DG, Lafferty ME. *Established Populations for Epidemiologic Studies of the Elderly.* Durham, NC: Duke Established Population for Epidemiological Studies; 1990;2. US Dept of Health and Human Services PHS NIH publication 90-495.

6. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc.* 1975;23:433-441.

7. Fillenbaum GG, Heyman A, Williams K, Prosnitz B, Burchett B. Sensitivity and specificity of standardized screens of cognitive impairment and dementia among elderly black and white community residents. *J Clin Epidemiol.* 1990;43:651-660.

8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition.* Washington, DC: American Psychiatric Association; 1980.

9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. *Neurology.* 1984;34:939-944.

10. Hughes CP, Berg L, Danziger WC, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566-572.

11. Baker FM. Dementing illness and black Americans. In: Jackson JS, ed. *The Black American Elderly: Research on Physical and Psychosocial Health.* New York, NY: Springer Publishing Co Inc; 1988.

12. Henderson AS. The risk factors for Alzheimer's disease: a review and a hypothesis. *Acta Psychiatr Scand.* 1988;78:257-275.

13. Kokmen E, Beard CM, Offord KP, Kurland LT. Prevalence of medically diagnosed dementia in a defined United States population: Rochester, Minnesota, January 1, 1975. *Neurology.* 1989;39:773-776.

14. Evans DA, Funkenstein H, Albert MS. Prevalence of Alzheimer's disease in a community population of older persons. *JAMA.* 1989;262:2551-2556.

Association of Decreased Paternal Age and Late-Onset Alzheimer's Disease

An Example of Genetic Imprinting?

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• Several studies have identified advanced maternal age as a risk factor for Alzheimer's disease. This study evaluated maternal and paternal age at birth of 237 patients with Alzheimer's disease, each of whom was matched to five control subjects based on sex, year of birth, survival age, and location of residence. It was found that decreased paternal age substantially increased the susceptibility to the common form of Alzheimer's disease that occurs after the age of 67 years, whereas advanced maternal age had a negligible effect on risk of Alzheimer's disease. The higher incidence of late-onset Alzheimer's disease among persons born to younger fathers is consistent with a genetic imprinting mechanism involving DNA methylation. The proposed model postulates a role for environmental agents in the pathogenesis of Alzheimer's disease and accounts for families that show an aggregation of cases but no apparent pattern of inheritance.

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Alzheimer's disease (AD) is a neurodegenerative dementing illness characterized by pervasive defects in cognition and personality; it affects an estimated 10% of the population older than 65 years.[1] The basic etiology of AD is unknown, although advanced age and a positive family history of dementia are two predominant risk factors. Several environmental agents, including head injury, slow viruses, and aluminum, have been implicated but have not yet been proved to play a role in the etiology and pathogenesis of AD.[2-7]

Numerous studies postulating a link between AD and Down syndrome[8-12] prompted investigations of maternal age at the birth of the subject, which has been identified as a strong risk factor for Down syndrome[13] and, thus, as a potential risk factor for AD. Four studies provided evidence that mothers of patients with AD are substantially older when their child is born than are mothers of control subjects,[14-17] whereas four other studies did not find this association.[18-21]

This study was undertaken to determine whether an association between AD and parental age at birth of the subject could be demonstrated in a comparatively large number of consecutively ascertained and rigorously diagnosed cases of AD, each of these patients being compared with five nondemented control subjects from the Framingham Study matched for sex, year of birth, and survival age. We hypothesized that if there is an effect of parental age on the incidence of AD, it would not likely be detectable in familial cases of AD (designated FAD) if liability for illness in these cases is caused by inherited defects that were already present in the parents' germ cell line before conception. Second, a parental age effect, if it exists, may be maternal or paternal in origin, depending on the particular genetic or nongenetic factors underlying the effect. For example, the incidence of many single-gene disorders is associated with advanced paternal age, whereas certain chromosomal aneuploidies are more prevalent in children born to older mothers.

SUBJECTS AND METHODS

Subjects

Genealogical data and family history of dementia were collected for 301 unrelated probands examined consecutively in the Memory Disorders Unit of the Massachusetts General Hospital, of whom 251 met National Institute for NINCDS-ADRDA criteria[22,23] for probable AD. Protocols for patient evaluation, informant interviews, and administration of questionnaire instruments are described elsewhere.[24] Preliminary data analysis showed that 14 of the probands with probable AD were missing parental age data for one or both parents, and these individuals were subsequently dropped from further analysis. The final total sample with AD from the Memory Disorders Unit consisted of 237 subjects (95 men and 142 women) born between 1895 and 1940. The mean (± SD) age at onset of dementia was 67.2±8.4 years (range, 42 to 86 years).

Control data were obtained from 8723 participants of the Framingham Study.[25] Approximately 5209 of these persons are adult residents of the town of Framingham, Mass, who were enrolled in a longitudinal study of health in 1950. Most of the original study members were the 4469 respondents of 6510 persons selected in a two-thirds stratified sampling of the adult population of the town. Another portion of this cohort, 740 men and women, were volunteers who were spouses of persons in the sample. Pertinent medical history, psychological, family history, lifestyle, and demographic data have been systematically collected over biennial examinations during this time. The remainder of the

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Framingham Study population comprises children of the original cohort who currently are participating in a parallel longitudinal study known as the Offspring Study. Dates of birth for parents of control subjects whose parents were also Framingham Study participants were obtained from their parents' records. Otherwise, this information was obtained from another database, which stored parental data collected in a previous study described by Schildkraut et al.[26]

For analytical purposes, the 237 subjects with AD were matched with five controls based on sex, year of birth, and a survival age variable. To improve the power of our statistical analyses by minimizing the SEs in the control group, we chose five controls (rather than one) for every case. The Framingham pool of subjects would not permit more controls per case without loss of cases owing to an insufficient number of matching controls. Furthermore, it has been shown that the increase in power is not substantial beyond four controls per case.[27] Specifically, age at onset of dementia in the patient with AD was matched with the censoring age (current age or age at death) in the control subjects. Control subjects were not demented at the time of censoring. If an insufficient number of controls were found to meet all three criteria, the matching algorithm selected controls who were born within 3 years of the case or whose censoring age was up to 3 years greater than the onset age of the case. With five matched controls for every case, the total control sample numbered 1185.

Analytical Procedures

Parental ages (age of mother and father, respectively, at time of subject's birth) were compared between AD cases and controls in two ways. In one method, mean maternal and paternal ages were calculated for each set of five matched controls and compared with the corresponding values for the cases using a paired-comparison *t* test, which tests whether the mean of the differences between the matched pairs is significantly different from zero.[28] Subgroup analysis was carried out by dividing subjects based on the mean onset age of AD (older or younger than 67.2 years) and family history of dementia of the AD cases, two criteria that may define distinct subtypes of AD.[29-31] Stratification by family history is less straightforward. A positive family history of dementia in a relative does not prove that the proband was genetically predisposed to AD because, for example, dementia could occur in two siblings by chance. Family and genetic studies suggest that AD in a proportion of cases may be transmitted as an autosomal dominant trait, particularly if onset occurs before the age of 65 years.[32] Thus, a case was defined as FAD only if either parent had AD. All other cases were considered to be sporadic (designated SAD).

To examine the interrelationship of paternal and maternal ages on development of AD, parental ages were also evaluated using conditional logistic regression for case-control designs.[33] This design permits the joint analysis of the effects of maternal and paternal ages and their interactions with other covariates on the development of AD to disentangle the correlation of mothers' and fathers' ages ($r = .77$ for AD cases and $r = .71$ for controls). These analyses were carried out using the PHGLM procedure in SAS, as described in the manual for an application to conditional logistic models with one case per matched set.[34]

Table 1.—Age of Parents at Subject's Birth for Patients With AD and Control Subjects According to Onset Age and Family History of Dementia of Probands With AD*

Group	No.	Mean Year of Birth	Maternal Age, y			Paternal Age, y		
			AD	Control	*P*	AD	Control	*P*
All	237	1916	27.4 ± 0.4	27.9 ± 0.2	NS	30.5 ± 0.5	31.6 ± 0.2	NS
Early onset (<67.2 y)	110	1923	27.9 ± 0.6	27.4 ± 0.2	NS	31.0 ± 0.7	30.4 ± 0.3	NS
Late onset (>67.2 y)	127	1911	27.0 ± 0.6	28.3 ± 0.3	.035	30.2 ± 0.7	32.5 ± 0.3	.003
FAD	81	1917	28.5 ± 0.7	28.4 ± 0.3	NS	31.4 ± 0.9	32.4 ± 0.4	NS
SAD	156	1916	26.8 ± 0.5	27.6 ± 0.2	NS	30.1 ± 0.6	31.2 ± 0.3	NS
Early onset, FAD	37	1923	29.4 ± 1.1	27.9 ± 0.4	NS	32.0 ± 1.4	31.0 ± 0.5	NS
Early onset, SAD	73	1923	27.1 ± 0.7	26.8 ± 0.3	NS	30.5 ± 0.8	29.8 ± 0.3	NS
Late onset, FAD	44	1912	27.8 ± 1.0	28.7 ± 0.4	NS	30.9 ± 1.3	33.5 ± 0.4	NS
Late onset, SAD	83	1911	26.5 ± 0.7	28.1 ± 0.3	.050	29.8 ± 0.8	32.0 ± 0.4	.019

* AD indicates Alzheimer's disease; NS, not significant; FAD, familial AD; and SAD, sporadic AD. Numbers are number of subjects with AD or number of matched sets. Values are mean ± SE.

Table 2.—Conditional Logistic Regression Analysis of Effect of Maternal and Paternal Age on Outcome of AD vs Control by Onset Age and Family History of Dementia of Probands With AD*

Group	No.	Maternal Age, y			Paternal Age, y			Model *P*
		5-y OR	95% CI	*P*	5-y OR	95% CI	*P*	
All	1422	1.04	0.89-1.23	NS	0.88	0.76-1.01	NS	NS
Early onset	660	1.07	0.83-1.37	NS	1.02	0.81-1.29	NS	NS
Late onset	762	1.01	0.82-1.25	NS	0.80	0.67-0.96	.019	.0053
Early onset, FAD	222	1.30	0.82-2.06	NS	0.89	0.55-1.42	NS	NS
Early onset, SAD	438	0.97	0.72-1.31	NS	1.07	0.82-1.40	NS	NS
Late onset, FAD	264	1.18	0.82-1.70	NS	0.71	0.51-0.99	.045	NS
Late onset, SAD	498	0.93	0.71-1.21	NS	0.85	0.68-1.06	NS	.037

* AD indicates Alzheimer's disease; OR, odds ratio for AD developing for every 5-year increase in maternal or paternal age; CI, confidence interval (for odds ratio); NS, not significant; FAD, familial AD; and SAD, sporadic AD. Numbers are sample size where the proportion of AD cases is one sixth of the sample.

RESULTS

The mean maternal and paternal ages at the time of the subject's birth were almost identical for patients with AD and control subjects (Table 1). However, at the time of the subject's birth, fathers of late-onset AD cases were significantly younger than fathers of control subjects by an average of 2.2 years ($P = .003$). A similar trend was observed for maternal age, but the difference was only 1.3 years ($P = .035$). Maternal and paternal ages were not significantly different among AD cases and controls in FAD or SAD subgroups. Stratification of subjects with AD and their corresponding matched controls by onset age group and family history showed that the paternal age effect is present only in patients with late-onset AD whose parents did not have AD. The difference in maternal age in this subset is smaller and only borderline significant ($P = .050$). Older paternal age among controls was observed in the group with late-onset FAD, but the difference was not significant because the sample size was only half as large as the group with late-onset SAD.

Conditional logistic models confirmed the presence of a significant paternal age effect in late-onset cases and suggests that the observed maternal age effect in the univariate analysis is probably due to the high collinearity between mothers' and fathers' ages (Table 2). Moreover, examination of the coefficients for this model reveals that paternal age has a 21-fold stronger effect than maternal age on the predicted outcome of AD vs control. The comparatively weaker maternal age effect shows a slight positive association with risk of AD. Relative risk of late-onset AD as a function of maternal and paternal age is shown in Fig 1.

COMMENT

The results of this study suggest that paternal age and, to a much lesser degree, maternal age influence an individual's susceptibility to the common form of AD that occurs after the age of 67 years. Moreover, in contrast to other studies that found an association between AD and advanced maternal age,[14-17] the data reported herein indicate that decreased paternal age increases the risk for AD. Our findings are based on data from 237 rigorously diagnosed and consecutively ascertained patients with AD who were matched to five control subjects each based on the year of birth, sex, survival age, and residence.

The mean parental ages for the cases and controls are in agreement with comparable data from other studies (Table 3). Careful inspection of these data revealed that parental ages in the control group in the Japanese study[17] were noticeably low, and the median parental ages of AD subjects in the original University of Washington study[14] were much higher than in other case series. Biased selection of cases and/or controls, social differences in childbearing patterns, or sampling error may account for these differences.

Failure to detect an association between AD and decreased paternal age in previous studies can be explained by several reasons. First, the effect was demonstrable only after removing early onset cases from the study population. Second, the number of late-onset AD cases in this study (124) exceeded the total subject population with AD in all but two other studies,[16,21] one of which found only a marginal advanced maternal age effect and did not examine paternal age.[16] Equal case and control samples of at least 220 persons each are required to detect a mean difference of 2.0 ± 7.5 years, assuming 5% error and 80% power. Third, none of the previous investigations of parental age accounted for censoring bias of controls, thus ignoring the possibility that some of these subjects may suffer dementia later in life. Fourth, this study is the first to assess maternal and paternal ages simultaneously using statistical methods to adjust for collinearity between mothers' and fathers' ages.

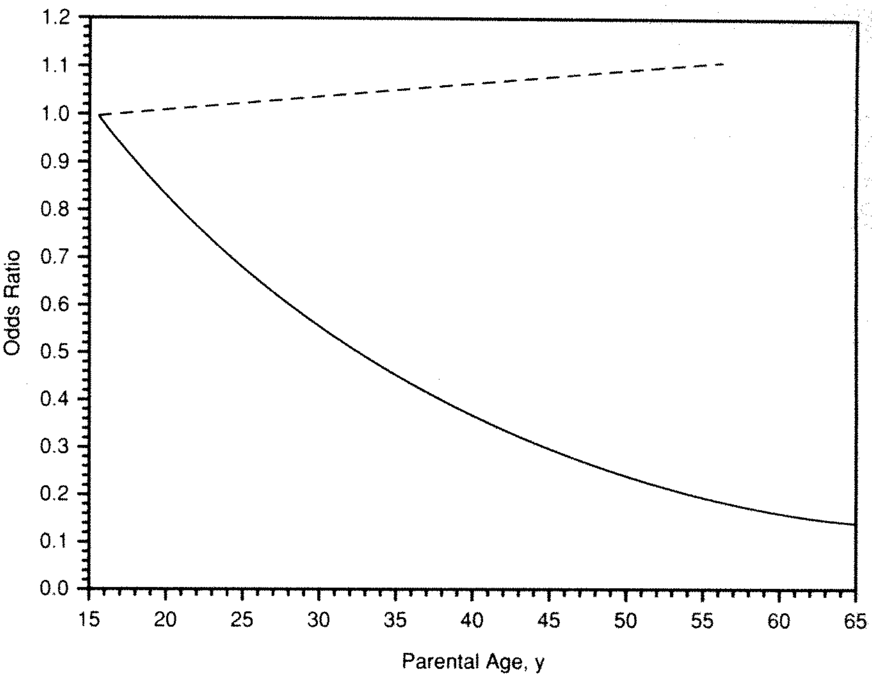

Fig 1.—Relative risk of late-onset Alzheimer's disease developing according to mother's (broken line) and father's (solid line) age at the time of birth. Separate risk curves for maternal and paternal age were calculated from the conditional logistic regression model for subjects with late-onset disease and matched controls (Table 2). The odds ratio equation for maternal age is $\mathrm{OR} = \exp(0.0021 \times \text{maternal age})$ where exp refers to the exponential function; the equation for paternal age is $\mathrm{OR} = \exp(-0.044 \times \text{paternal age})$. The odds ratio at the age of 15 years was standardized to 1.

However, there are several caveats in the interpretation of our findings. First, the observation of advanced maternal age in AD cases in other studies needs to be reexamined in those and other populations using a sufficient number of patients with AD and appropriately matched controls. All of the published studies of parental age, including our own, were performed on a clinic-based series of subjects, which may not be representative of patients with AD in the general population. Longitudinal studies of the dementia status of a large cohort of elderly subjects, including their siblings,[35] would allow alternative study designs of parental age, including unbiased evaluation of birth order. Second, further examination of the results in Table 1 suggests that parental ages are not different between early-onset and late-onset AD cases. However, it is misleading to conclude that there are no parental age differences between early-onset and late-onset AD cases simply because the mean ages are the same. To compare these two groups appropriately, the cases would need to be matched for year of birth. In addition, controls matched to late-onset AD cases have significantly greater maternal ($t = 2.45$, $P = .015$) and paternal ($t = 4.91$, $P < .001$) ages than controls matched to early-onset cases. Although these patterns may suggest a biased sample of control subjects in the late-onset group, the parental age difference among controls is more likely related to secular trends in year of birth. Early-onset cases and controls had a mean birth year of 1923 (range, 1907 to 1940), which is significantly greater than the mean of 1911 (range, 1895 to 1919) for the late-onset subjects ($t = 16.31$, $P < .001$). The mean parental ages for the control groups are consistent with secular trends for parental age in the Framingham cohort (Fig 2). Even though this secular trend persists, our subjects are matched on year of birth, and thus, our conclusions should not be affected by this secular trend. Third, the results of our study suggest, but do not rule out, that the parental age effect has a uniquely paternal origin. If the effect is partially or totally maternal, several other hypotheses regarding the maternal-fetal environmental (eg, toxic or infectious exposure and maternal immune response) or maternal (cytoplasmic or mitochondrial) inheritance must be considered.

The studies showing significantly greater maternal age in AD cases are puzzling because the premise underlying the hypothesis linking maternal age to both Down syndrome and AD is not entirely valid. The frequency of chromosomal nondisjunction, the biological mechanism causing most cases of Down syndrome and other trisomic conditions, increases with maternal age.[36]

Table 3.—Maternal and Paternal Ages Among AD Cases and Controls Reported in Previous Studies*

	Cases			Controls			
Study	**No.**	**Maternal Age, y**	**Paternal Age, y**	**No.**	**Maternal Age, y**	**Paternal Age, y**	**Comments**
Cohen et al[14]	80	35.5 ± 1.4	38.0 ± 1.4	590	27.0	. . .	Median values reported; all controls born in 1907
Whalley et al[15]	69	30.6 ± 0.7	32.2 ± 0.8	207	28.6 ± 0.4	30.8 ± 0.5	Each case was date-of-birth matched with 3 controls
Corkin et al[18]	36	27.7	30.8	34	27.4	29.4	Controls were 12 spouses and 22 unrelated volunteers
Heyman et al[19]	36	28.6	33.3	36	28.4	31.9	Cases matched to spouses
English and Cohen[20]	69	29	. . .	93	27-28	. . .	Median values estimated from distribution data; includes 2 groups of controls: spouses and spouses of patients with Parkinson's disease
Amaducci et al[16]	116	30.9	. . .	116/97	29.1/28.9	. . .	Cases age and sex matched to 1 hospital control and 1 population control
White et al[21]	98	29.1 ± 7.1	34.2 ± 8.3	92 200	27.5 ± 8.4 30.0 ± 6.4	32.9 ± 8.4 34.7 ± 7.7	SD reported; paternal age of AD cases based on sample size of 100; secondary AD cases (14 maternal ages and 13 paternal ages) excluded; control groups: line 1, normal siblings; line 2, sample selected from births recorded in same period as cases in 1 county of Minnesota
Urakami et al[17]	77	26.6 ± 6.6	31.4 ± 8.6	35	23.9 ± 4.8	26.3 ± 5.6	SD reported
Present study	237	27.4 ± 0.4	30.5 ± 0.5	1185	27.9 ± 0.2	31.6 ± 0.2	. . .

*AD indicates Alzheimer's disease. Values are mean ± SE unless otherwise noted.

However, chromosome studies of subjects with AD do not show any consistent abnormal findings other than those associated with normal aging.[37] Thus, there is no cytogenetic basis for increased frequency of AD with advanced maternal age. Furthermore, the advanced maternal age hypothesis presumes that the defect underlying the clinical, neuropathological, and familial traits common to AD and Down syndrome is on chromosome 21. However, the only direct evidence implicating chromosome 21 in the pathogenesis of AD is identification of genetic linkage between the gene for a rare, early onset, autosomal dominant form of AD and anonymous DNA markers that are located outside of the chromosomal region associated with Down syndrome,[38-41] as well as two studies showing triplication of chromosome 21 genes in randomly selected patients with AD,[42,43] but these latter results have been disputed.[44-46]

GENETIC HYPOTHESIS FOR PATERNAL AGE EFFECT

An explanation of the association between AD and decreased paternal age must account for the observation of this relationship occurring only in late-onset cases and the fact that transmission of uniquely paternal risk factors to offspring occurs only through the germ cell line. Thus, exposure to environmental agents is unlikely the cause of the paternal age effect. A growing body of evidence suggests that the early onset form of AD is an autosomal dominantly transmitted trait,[32] whereas AD in a proportion of individuals with late-onset disease may have other causes.[24,31] Lack of a paternal age effect among patients with SAD probably indicates that our classification scheme for FAD and SAD is not robust. Distinction of noninherited cases will continue to be difficult until a genetic or other biological marker is identified.

Although persons with SAD presumably have not inherited an abnormal AD gene per se, they may still inherit increased predisposition to disease through a particular parent. This type of transmission is called "genetic imprinting."[47] It has been postulated that imprinting does not cause a mutation in the DNA, but rather an alteration in the function of DNA that may last the lifetime of the individual.[47] Compelling evidence has been accumulating from experimental studies in transgenic mice that gene activity can be altered in alleles originating from a particular parent by methylation or demethylation of DNA.[48-52] Experimental evidence in human cells growing in culture indicates that there is a concomitant loss of the number of methylated sites on DNA and gene expression with increasing numbers of cell divisions. This age-related phenomenon is accelerated when even young cells are treated with azacytidine, a compound that enhances demethylation.[53] Sperm DNA, which is highly methylated except for a few spared genes,[49] is more likely to have undergone progressive demethylation than DNA in an ovum from a woman of the same age because male germ cells undergo many more cell divisions than female germ cells. To illustrate this point, at sexual maturity female germ cells have undergone two divisions. It has been estimated that the number of cell divisions in spermatogenesis is 30 at puberty and increases at the rate of 23 per year thereafter.[54] Thus, at the age of 35 years, for example, male germ cells have undergone approximately 540 divisions.

How might genomic imprinting be responsible for cases of late-onset AD, and how would it account for the tendency for these subjects to have younger fathers at the time of their birth? It has been postulated that AD is a sequela of the aging process.[55-57] Numerous genes

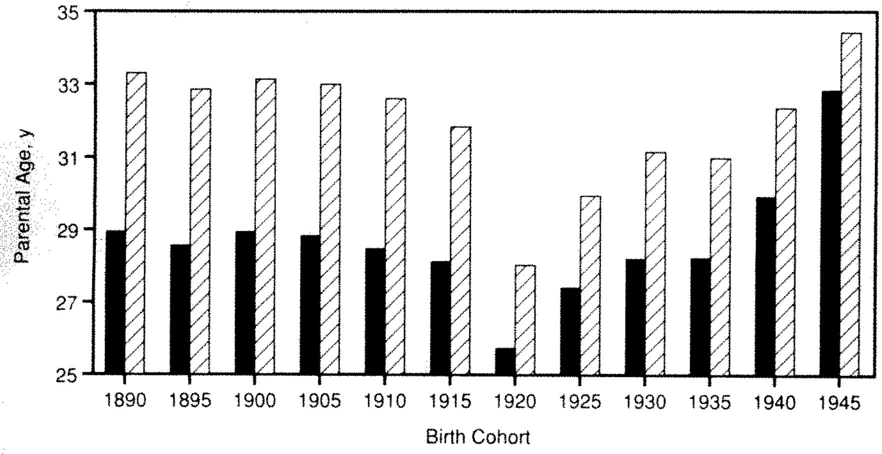

Fig 2.—Mean maternal (solid bars) and paternal (shaded bars) ages among 7559 subjects in the Framingham Study born between 1890 and 1949 by 5-year cohorts.

are likely involved in aging,[58] and it is conceivable that alteration in the expression of one or more of them could result in the AD phenotype. Normal development of the central nervous system depends on appropriately timed expression of many genes from embryonic life until adulthood. Complex systems like the brain must have a myriad of genetic regulation mechanisms, and evidence from studies of other inherited neurological diseases that show parental sex effects, including Huntington's disease, myotonic dystrophy, and neurofibromatosis, suggests that DNA methylation may be involved.[47,59,60]

Let us presume that most persons will suffer AD if they do not succumb to other causes before they reach the age at which they would have onset of symptoms, and that pathogenesis can be accelerated or retarded by methylation and demethylation of the genes involved. If protection against AD requires expression of certain genes early in life, it follows that a person born to a young father is more likely to have a higher proportion of methylated and hence inactive genes, including genes that, when active, protect against AD, than a person born to an older father. Therefore, this person has a higher risk of AD developing later in life. However, there must be an additional mechanism for the determination of onset, which usually occurs after the age of 65 years. Thus, this model predicts not only that the pathogenesis of AD begins early in life, but also that a second event, such as demethylation of the same or another set of genes later in life, is necessary for disease to occur. The involvement of environmental agents or other nongenetic risk factors in the second event would explain the low concordance rate for AD among monozygotic twins.[61-64]

A genetic imprinting model for AD would be consistent with the sporadic nature of most cases if the probability of having demethylated genes, and hence protection against AD, is high or if methylation is necessary but not sufficient for development of disease. This hypothesis could also account for families that show an aggregation of cases but no apparent transmission or inheritance pattern,[32] because the methylation states of identical alleles among parents and offspring would not necessarily be the same. However, we emphasize that the above arguments implicating DNA methylation are speculative. It is reasonable to expect that an imprinting mechanism other than methylation contributes to the pathogenesis of AD, but little is known about these processes.

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References

1. Evans DA, Funkenstein HH, Albert MS, et al. Prevalence of Alzheimer's disease in a community population of older persons. *JAMA.* 1989;262:2551-2556.
2. Goudsmit J, Morrow CH, Asher DM, et al. Evidence for and against transmissibility of Alzheimer's disease. *Neurology.* 1980;30:945-950.
3. Mortimer JA, French LR, Hutton JT, Schuman LM. Head injury as a risk factor for Alzheimer's disease. *Neurology.* 1985;35:264-267.
4. Crapper McLachlan DR. Aluminum and Alzheimer's disease. *Neurobiol Aging.* 1986;7:525-532.
5. Birchall JD, Chappall JS. Aluminum, chemical physiology, Alzheimer's disease. *Lancet.* 1988;2:1008-1010.
6. Manuelidis EE, de Figueredo JM, Kim JH, Fritch WW, Manuelidis L. Transmission studies from blood of Alzheimer disease patients and healthy relatives. *Proc Natl Acad Sci U S A.* 1988;85:4898-4901.
7. Martyn CN, Barker DJP, Osmond C, Harris EC, Edwardson JA, Jacey RF. Geographical relation between Alzheimer's disease and aluminum in the drinking water. *Lancet.* 1989;1:59-62.
8. Haberland G. Alzheimer's disease in Down's syndrome. *Acta Neurol Belg.* 1969;69:369-380.
9. Heston LL. Alzheimer's disease, trisomy 21, and myeloproliferative disorders: associations suggesting a genetic diathesis. *Science.* 1977;196:322-323.
10. Ellis WG, McCulloch JR, Corley CL. Presenile dementia in Down's syndrome: ultrastructural identity with Alzheimer's disease. *Neurology.* 1974;24:101-106.
11. Wisniewski K, Howe J, Williams DG, Wisniewski HM. Precocious aging and dementia in patients with Down's syndrome. *Biol Psychiatry.* 1978;13:619-627.
12. Mann DMA. The pathological association between Down syndrome and Alzheimer disease. *Mech Ageing Dev.* 1988;43:99-136.
13. Penrose LS. The relative effects of paternal and maternal age in mongolism. *J Genet.* 1933;27:219-224.
14. Cohen D, Eisdorfer C, Leverenz J. Alzheimer's disease and maternal age. *J Am Geriatr Soc.* 1982;30:656-659.
15. Whalley LJ, Carothers AD, Collyer S, De Mey R, Frackiewicz A. A study of familial factors in Alzheimer's disease. *Br J Psychiatry.* 1982;140:249-256.
16. Amaducci LA, Fratiglioni L, Rocca WA, et al. Risk factors for clinically diagnosed Alzheimer's disease: a case-control study of an Italian population. *Neurology.* 1986;36:922-931.
17. Urakami K, Adachi Y, Takahashi K. A community-based study of parental age at the birth of patients with dementia of the Alzheimer type. *Arch Neurol.* 1989;46:38-39.
18. Corkin S, Growdon JH, Rasmussen SL. Parental age as a risk factor in Alzheimer's disease. *Ann Neurol.* 1983;13:674-676.
19. Heyman A, Wilkinson WE, Hurwitz BJ, et al. Alzheimer's disease: genetic aspects and associated clinical disorders. *Ann Neurol.* 1983;14:507-515.
20. English D, Cohen D. A case-control study of maternal age in Alzheimer's disease. *J Am Geriatr Soc.* 1985;33:167-169.
21. White JA, McGue M, Heston LL. Fertility and parental age in Alzheimer's disease. *J Gerontol.* 1986;41:40-43.
22. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42:1097-1105.
23. McKhann G, Drachmann D, Folstein M, Katzman R, Price D, Stadlan D. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-945.
24. Farrer LA, O'Sullivan DM, Cupples LA, Growdon JH, Myers RH. Assessment of genetic risk for Alzheimer's disease among first-degree relatives. *Ann Neurol.* 1989;25:485-493.
25. Dawber TR, Meadors GF, Moore FE. Epidemiological approaches to heart disease: the Framingham Study. *Am J Public Health.* 1951;41:279-286.
26. Schildkraut JM, Myers RH, Cupples LA, Kiely DJ, Kannel WB. Coronary risk associated with age and sex of parental heart disease in the Framingham study. *Am J Cardiol.* 1989;64:555-

559.

27. Gail M, Williams R, Byar DP, Brown C. How many controls? *J Chronic Dis.* 1976;29:723-731.

28. Sokal RR, Rohlf RJ. *Biometry.* 2nd ed. New York, NY: WH Freeman & Co; 1981.

29. Chui HC, Teng EL, Henderson VW, Moy AC. Clinical subtypes of dementia of the Alzheimer type. *Neurology.* 1985;35:1544-1550.

30. Mayeux R, Stern Y, Spanton S. Heterogeneity in dementia of the Alzheimer type: evidence of subgroups. *Neurology.* 1985;35:453-461.

31. Farrer LA, Myers RH, Cupples LA, et al. Transmission and age-at-onset patterns in familial Alzheimer's disease: evidence for heterogeneity. *Neurology.* 1990;40:395-403.

32. St George-Hyslop PH, Myers RH, Haines JL, et al. Familial Alzheimer's disease: progress and problems. *Neurobiol Aging.* 1989;10:417-425.

33. Breslow NE, Day NE, Halvorsen KT, Prentice RL, Sabai C. Estimation of multiple relative risk functions in matched case-control studies. *Am J Epidemiol.* 1978;108:299-307.

34. *SAS User's Guide: Statistics.* Cary, NC: SAS Inc; 1986.

35. White L, Wolf PA, Farmer M, et al. Neuropsychologic test performance in later life: a cross-sectional study of the Framingham Heart Study cohort. *Am J Epidemiol.* 1983;118:444. Abstract.

36. Hassold TJ, Jacobs PA. Trisomy in man. *Annu Rev Genet.* 1984;18:69-67.

37. Buckton KE, Whalley LJ, Lee M, Christie JE. Chromosome changes in Alzheimer's presenile dementia. *J Med Genet.* 1983;20:46-51.

38. St George-Hyslop P, Tanzi RE, Polinsky RJ, et al. The genetic defect causing familial Alzheimer's disease maps on chromosome 21. *Science.* 1987;235:885-890.

39. Goate AM, Haynes AR, Owen MJ, et al. Predisposing locus for Alzheimer's disease on chromosome 21. *Lancet.* 1989;1:352-355.

40. Van Broeckhoven C, Van Hul W, Backhovens H, et al. The familial Alzheimer's disease gene is located close to the centromere on chromosome 21. *Am J Hum Genet.* 1988;43(suppl):A205. Abstract.

41. St George-Hyslop PH, Haines JL, Farrer LA, et al. Genetic linkage studies suggest that Alzheimer's disease is not a single homogeneous disorder. *Nature.* 1990;347:194-197.

42. Delabar JM, Goldgaber D, Lamour Y, et al. β Amyloid gene duplication in Alzheimer's disease and karyotypically normal Down syndrome. *Science.* 1987;235:1390-1392.

43. Schweber M, Tuson C, Shiloh R, Ben-Neriah Z. Triplication of chromosome 21 material in Alzheimer's disease. *Neurology.* 1987;37(suppl 1):222. Abstract.

44. St George-Hyslop PH, Tanzi RE, Polinsky RJ, et al. Absence of duplication of chromosome 21 genes in familial and sporadic Alzheimer's disease. *Science.* 1987;238:664-666.

45. Tanzi RE, Bird ED, Latt SA, Neve RL. The amyloid β protein gene is not duplicated in brains from patients with Alzheimer's disease. *Science.* 1987;238:666-669.

46. Berman M, Lee G, Selkoe DJ. Gene dosage of the amyloid β precursor protein in Alzheimer's disease. *Science.* 1987;238:669-671.

47. Hall JG. Genomic imprinting: review and relevance to human diseases. *Am J Hum Genet.* 1990;46:857-873.

48. Hadchouel M, Farza H, Simon D, Tiollias P, Poucel C. Maternal inhibition of hepatitis B surface antigen gene expression in transgenic mice correlates with de novo methylation. *Nature.* 1987;329:454-456.

49. Monk M, Boubelik M, Lehnert S. Temporal and regional changes in DNA methylation in the embryonic, extraembryonic and germ cell lineages during mouse development. *Development.* 1987;99:371-382.

50. Reik W, Collick A, Norris ML, Barton SC, Surani MAH. Genomic imprinting determines methylation of parental alleles in transgenic mice. *Nature.* 1987;328:248-251.

51. Sapienza C, Peterson AC, Rossant J, Balling R. Degree of methylation of transgenes is dependent on gamete of origin. *Nature.* 1987;328:251-254.

52. Swain JL, Stewart TA, Leder P. Parental legacy determines methylation and expression of an autosomal transgene: a molecular mechanism for parental imprinting. *Cell.* 1987;50:719-727.

53. Holliday R. A different kind of inheritance. *Sci Am.* June 1989:60-73.

54. Vogel F, Rathenberg R. Spontaneous mutation in man. *Adv Hum Genet.* 1975;5:223-318.

55. Berg L. Does Alzheimer's disease represent an exaggeration of normal aging? *Arch Neurol.* 1985;42:737-739.

56. Mann DMA, Yates PO, Marcyniuk B. Alzheimer's presenile dementia, senile dementia of the Alzheimer type and Down's syndrome in middle age form an age related continuum of pathological changes. *Neuropathol Appl Neurobiol.* 1985;10:185-207.

57. Brayne C, Calloway P. Normal ageing, impaired cognitive function, and senile dementia of the Alzheimer's type: a continuum? *Lancet.* 1988;1:1265-1267.

58. Farrer LA. Genetic neurodegenerative disease models for human aging. In: Rothstein M, ed. *Review of Biological Research in Aging.* New York, NY: Alan R Liss Inc; 1987;3:163-189.

59. Ridley RM, Frith CD, Crow TJ, Conneally PM. Anticipation in Huntington's disease is inherited through the male line but may originate in the female. *J Med Genet.* 1988;25:589-595.

60. Reik W. Genomic imprinting: a possible mechanism for the parental origin effect in Huntington's chorea. *J Med Genet.* 1988;25:805-808.

61. Davidson EA, Robertson EE. Alzheimer's disease in one monozygotic twin. *J Neurol Neurosurg Psychiatry.* 1955;35:707-722.

62. Jarvik LF, Ruth V, Matsuyama SS. Organic brain syndrome and aging: a six-year follow-up of surviving twins. *Arch Gen Psychiatry.* 1980;37:280-286.

63. Cook RH, Schneck SA, Clark DB. Twins with Alzheimer's disease. *Arch Neurol.* 1981;38:300-301.

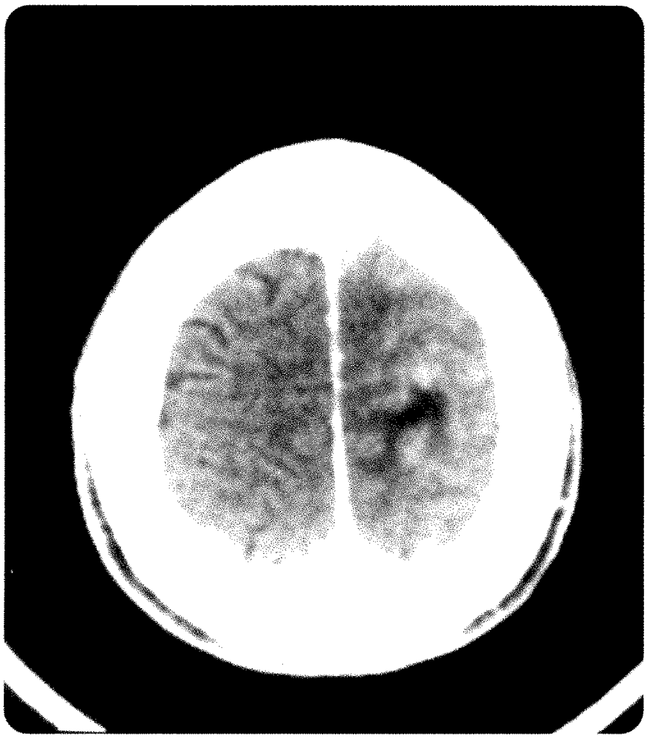
64. Nee LE, Eldridge R, Sunderland T, et al. Dementia of the Alzheimer type: clinical and family study of 22 twin pairs. *Neurology.* 1987;37:359-363.

THE DECISION IS YOURS.

COMPARE.

THE CASE: A 40-year-old man presented with a 2-month history of involuntary muscle contractions of the right arm and mild weakness of the left leg.

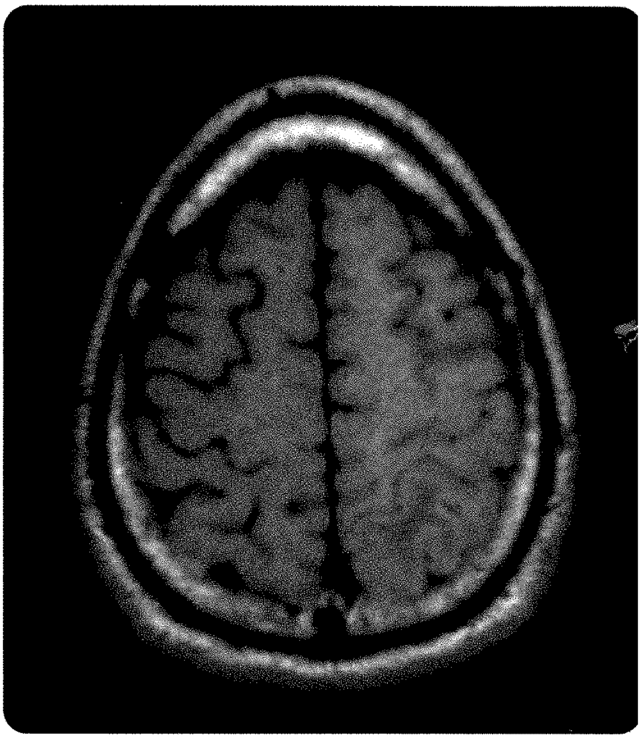
First there was CT.



Contrast CT scan shows an area of low attenuation in the left parietal lobe. A questionable focus of contrast is seen, but this may represent cerebral cortex.

Images courtesy of Michael R. Ross, MD, Stanford University Medical Center, Stanford, California

Then MRI.



T1-weighted (TR 800/TE 20) unenhanced MR image, obtained with a 1.5-T imager, shows subcortical hypointensity in the left posterior parietal lobe. The surrounding sulci appear to be compressed, but a mass is not clearly appreciated.

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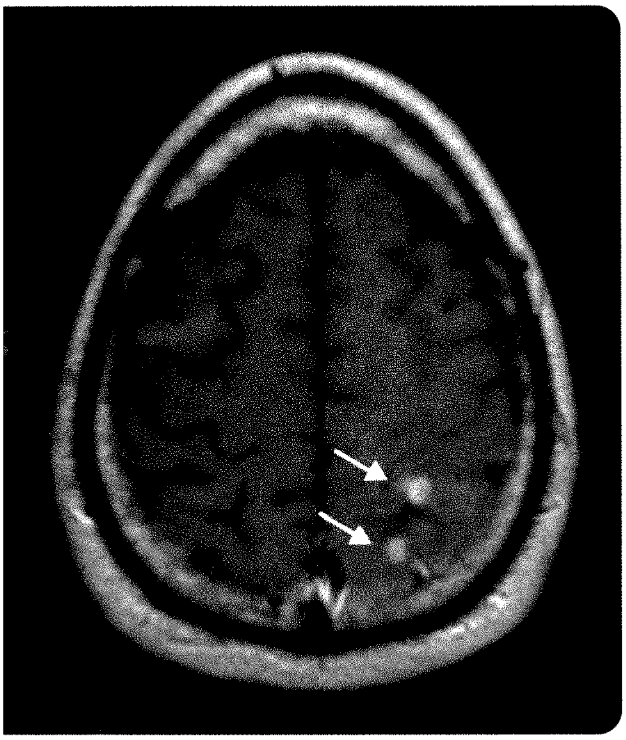
AND CONTRAST.

ow, *Magnevist*®-
nhanced MRI lets
ou see even more.

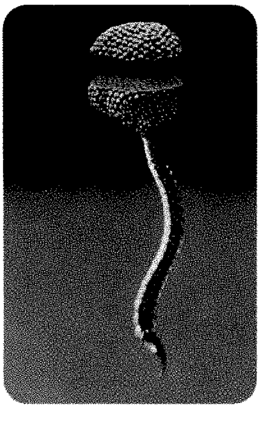


1-weighted (TR 800/TE 20) image enhanced with AGNEVIST® injection reveals two discrete nodules rrows). This nodular enhancement is highly uggestive of a primary brain tumor, which was onfirmed upon biopsy to be an astrocytoma.

Magnevist®
(gadopentetate
dimeglumine 469.01 mg/mL)
INJECTION

NOTHING LOCATES LESIONS BETTER

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.



Well tolerated[1] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCE: 1. Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 μg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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BERLEX IMAGING®

A 'Stress' Test for Memory Dysfunction

Electrophysiologic Manifestations of Early Alzheimer's Disease

Leyla deToledo-Morrell, PhD; Susan Evers; Thomas J. Hoeppner, PhD; Frank Morrell, MD, MSc; David C. Garron, PhD; Jacob H. Fox, MD

• Long-latency event-related potentials (P300) were assessed in patients wth early probable Alzheimer's disease (AD), age-matched controls, and young adults during a task that imposed various degrees of demand on memory. Although patients with AD did not differ from age-matched controls when one item had to be remembered, their P300 potential was dramatically reduced in amplitude or absent with increasing memory load. Aged controls did not differ from young adults on this mesuer. P300 latency, however, did not differentiate patients with AD. Thus, electrophysiological abnormalities detected in the context of mnemonic demand may provide a sensitive marker of the early stages of probable AD.

(*Arch Neurol.* 1991;48:605-609)

The detailed investigations of Sutton et al[1] and of Donchin and colleagues[2-8] have shown that the P300 component of long-latency, endogenous, event-related potentials (ERPs) is intimately related to information-processing activities in normal young adults. The so-called P300 consists of a positivity, most prominently recorded from posterior regions of the scalp, that peaks at approximately 300 milliseconds following stimulus onset. With complex stimuli, the peak may occur later. In general, the above-cited research has demonstrated that P300 latency is an index of the time required for the categorization of events and is quite independent of the time needed for response selection and execution processes. On the other hand, P300 amplitude was shown to depend on the amount of information-processing activity evoked by a stimulus and to be especially sensitive to alterations in the subject's expectancy of an event.[9]

The P300 component of ERPs has been extensively used to study age-related[10-15] and disease-induced[14,16-20] alterations in cognitive function. In recent years, however, there has been some disappointment in the utility of the P300 as a diagnostic tool in clinical settings. One reason for this disappointment may be that most clinical studies have relied on the auditory oddball paradigm as the task to elicit ERPs and a delay in P300 latency as the crucial measure for diagnosing alterations in cognitive function and dementia. In the auditory oddball paradigm, two tones are presented with different probabilities and the subject has to count (or make a motor response to) the infrequently occurring stimulus. However, evidence indicates that (1) increases in P300 latency occur as a function of aging per se in nondemented adults,[11-13,15] and (2) an increase in P300 latency is not a very sensitive index of memory dysfunction during the *very early* stages of dementia[20,21] when a sensitive diagnostic tool would be most useful to the clinician. For example, in the Patterson et al[21] study, which employed the auditory oddball paradigm, only 13% of demented patients could be correctly classified on the basis of P300 latency. Most important, however, is the fact that delays in P300 latency have been observed in nondementing disorders such as depression and schizophrenia as well.[19]

Recently, reports from a number of laboratories, including ours, have indicated that the utility of the P300 for diagnosing specific types of memory disorders can be much improved if ERPs are recorded in the context of tasks that impose some demand or "stress" on memory function.[22-26] These studies, which showed that the P300 is much reduced in amplitude (or not present at all) during tasks with a strong mnemonic component in patients with memory disorders, underscore the importance of the behavioral tasks employed in the clinic to elicit electrophysiologic abnormalities in different patient populations. Given that P300 amplitude has been shown to be directly related to the degree of recall in young subjects,[6,7] it makes sense that this factor, rather than P300 latency, might provide a more sensitive marker of memory dysfunction.

We now report that alterations in P300 amplitude recorded during a task that imposes different degrees of demand or stress on mnemonic function provide a sensitive electrophysiologic marker of the very early stages of probable Alzheimer's disease (AD). In our hands, alterations in P300 latency did not differentiate patients with AD from age-matched controls.

SUBJECTS AND METHODS

The data reported herein were obtained from six patients with presumed early AD ranging in age from 67 to 76 years (mean age, 72 years), seven age-matched controls ranging in age from 65 to 76 years (mean age, 71 years), and 11 young adults ranging in age from 22 to 38 years (mean age, 27 years). The patients with AD consisted of four right-handed women and two right-handed men, recruited through the Rush Alzheimer's Disease Center (Chicago, Ill) from among those who met the National Institute of Neurological Disorders and Stroke/Alzheimer's Disease and Related Disorders Association criteria for probable AD.[27] They had dementia documented by clinical and psychometric examination, and they had deficits in at least two areas of cognition with the *major* deficit being mnemonic in nature. Only patients with mild dementia, as defined by a Mini Mental State[28] score of 20 or greater, were included in this study. The Mini Mental State scores of our patients ranged from 24 (only one patient) to 21, with a mean of 22.5. Dementia and memory scores for individual patients with AD are presented in the Table.[29] Patients who showed evidence of disturbed consciousness or evidence of other neurologic or systemic illness that can produce dementia, who had a history of alcohol/substance abuse, or who had a history of a major psychiatric disorder were excluded from the study.

The age-matched controls consisted of five right-handed women and two right-handed men who were recruited primarily from the Rush Medical Center Volunteer Office and from among spouses of patients with AD. They were all in good health and led active lives. The young adult subjects (five right-

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From the Departments of Neurological Sciences (Drs deToledo-Morrell, Fox, Hoeppner, and Morrell and Ms Evers) and Psychology and Social Sciences (Drs deToledo-Morrell and Garron), and the Rush Alzheimer's Disease Center (Dr Fox), Rush Medical College, Chicago, Ill.

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Reprint requests to Rush Medical College, 1653 W Congress Pkwy, Chicago, IL 60612 (Dr deToledo-Morrell).

handed men, one left-handed man, and five right-handed women) were mostly medical students, electroencephalography technicians, and junior faculty members.

If subjects normally wore corrective lenses, they were asked to keep them on during the test. Informed consent was obtained from all subjects according to the rules of the Human Investigation Committee of Rush Medical College.

Stimuli and Procedure

All aspects of experimental control and data collection were carried out with a computer system (Pearl System, PDP-11/40) designed and built at the Cognitive Psychophysiology Laboratory of the University of Illinois, Champaign. The ERPs were recorded during a modified Sternberg[30] memory scanning task. On a television monitor, subjects were shown a set of letters to be studied and remembered, memory set size varying from one to five letters. During the "study period," the letters remained on the screen for 60 seconds. After each study period for a given set size, single letters were presented one at a time for 700 milliseconds and subjects were asked to press one key with a given hand if the letter was from the memory set, and a second key with the other hand if it was any other letter of the alphabet. The hand used for each type of response was counterbalanced across subjects. Previously memorized letters (target) were presented with a probability of 24%. One hundred single-letter presentations or trials were used for each memory set size, the intertrial interval averaging 3500 milliseconds. The order of testing with each memory set size was counterbalanced, except that because of the patients with AD, testing was never started with a memory set size of five letters. Thus, as modified in our hands, the Sternberg task provides a measure of recent memory rather than immediate memory.

Recording and Quantification of the P300 Potential

Using the International 10-20 System,[31] silver chloride electrodes (Grass) were affixed with collodion at the following regions: P_z (midline parietal), F_z (midline frontal), P_3 (left parietal), P_4 (right parietal), A_1 (left ear lobe), A_2 (right ear lobe), and an additional cephalic location to be used as ground. For recording, P_z and F_z were referred to linked ears, P_3 and P_4 each to ipsilateral ear since, in this case, a linked ear reference would have been inadequate for detecting lateralized abnormalities. Eye movements were monitored by recording between two electrodes placed above and below the right eye. Trials contaminated by eye blinks were eliminated. Subjects were given extensive instructions to control their eye blinks while a stimulus was on the screen and to blink only between trials. Since most subjects, including patients with AD, complied with these instructions well, contamination by eye-movement artifact was not much of a problem in our experiments. For any given individual subject, no more than six trials were ever eliminated.

Electrode impedance was kept equal to or below 3 kΩ. Bioelectric activity was amplified using amplifiers (Grass model 7P511 with filter settings between 0.1 and 100 Hz) and was digitized at the rate of 200 samples per second for 100 milliseconds prior to stimulus onset (which served as baseline) and for 900 milliseconds following stimulus onset. Single trial data were stored on magnetic tape for later off-line analyses. P300 amplitude and latency were automatically calculated by the computer. P300 amplitude was defined as the peak positivity occurring between 250 and 750 milliseconds following stimulus onset and was measured from baseline. P300 latency was defined as the time from stimulus onset to the peak positivity.

Dementia and Memory Scores for Patients With Probable Alzheimer's Disease

Patient No./Age, y/Sex	Folstein Mini Mental Score (Maximum = 30)	Mattis Dementia Rating Scale Scores	
		Total (Maximum = 144)	Memory Subscale (Maximum = 25)
1/73/M	21	123	12*
2/70/M	23	126	18*
3/74/F	21†	124	11*
4/76/F	23	118*	14*
5/67/F	23	119*	12*
6/74/F	24	132	16*

*Refers to scores on the Mattis[29] Dementia Rating Scale that are in the impaired range defined as 2 SDs below the mean.

†Average of two scores obtained close to the time of electrophysiologic testing.

Statistical Analyses

Group differences for each type of measure collected (such as P300 latency or amplitude, reaction time, and choice accuracy) were assessed by separate analyses of variance with ϵ correction for nonsphericity.[32] Further comparisons between two means consisted of two-tailed t tests for independent samples with probabilities corrected for the number of tests performed. A significance level of P less than .05 was set for all tests.

RESULTS

Electrophysiologic data described herein are based on P300 potentials recorded from midline parietal regions (P_z), since this report is not concerned with hemispheric asymmetries. Hemispheric differences in ERPs elicited during hemisphere-specific tasks are described elsewhere.[33]

Averaged ERPs for individual subjects elicited by target letters are presented in Fig 1. The top part of Fig 1 shows ERPs obtained from a typical elderly control subject when memory set sizes of one or five letters were used. Figure 1, center and bottom, provides a comparison of ERPs recorded from two patients with probable AD under the same conditions. Note that patients with AD had a well-formed P300 that was comparable to that of age-matched controls when a memory set size of one letter was used. With a memory set size of five letters, however, the P300 potential was absent or dramatically reduced in amplitude in the same patients. This effect was seen in all six patients with AD studied. A comparison of P300 amplitude (Fig 2) in patients with AD and age-matched controls (analysis of variance) showed a significant group difference ($P<.001$) as well as a memory load effect ($P<.001$). Further comparisons revealed that patients with AD did not differ from age-matched controls when one letter had to be remembered, but they showed significantly reduced P300 amplitudes with memory loads of two letters or more. There was no age effect per se on P300 amplitude in that aged controls did not differ from young adults.

In marked contrast to the amplitude measure, patients with AD did not differ from age-matched controls in P300 latency (Fig 3), but both showed significantly delayed potentials compared with young adults ($P<.005$ for the age effect). It could be argued that the latency measure for trial blocks requiring memory loads of four or five letters was not too accurate for patients with AD since it was difficult to detect a peak. However, even with a memory load of one or two items, when the P300 potential was well formed in patients with AD, its latency was comparable to that of age-matched controls. The age-related increase in P300 latency found in our study, which approximates 1.5 ms/y, is comparable to that reported in the literature.[11-13,15]

In our experiment, in addition to ERPs, two behavioral measures, namely reaction time and choice accuracy, were recorded. With respect to reaction time (Fig 4), patients with AD responded just as rapidly as age-matched controls to target letters when a memory load of one letter was required. This result indicates that patients with AD did not have any motor dysfunction. However, they were much slower in responding than age-matched controls

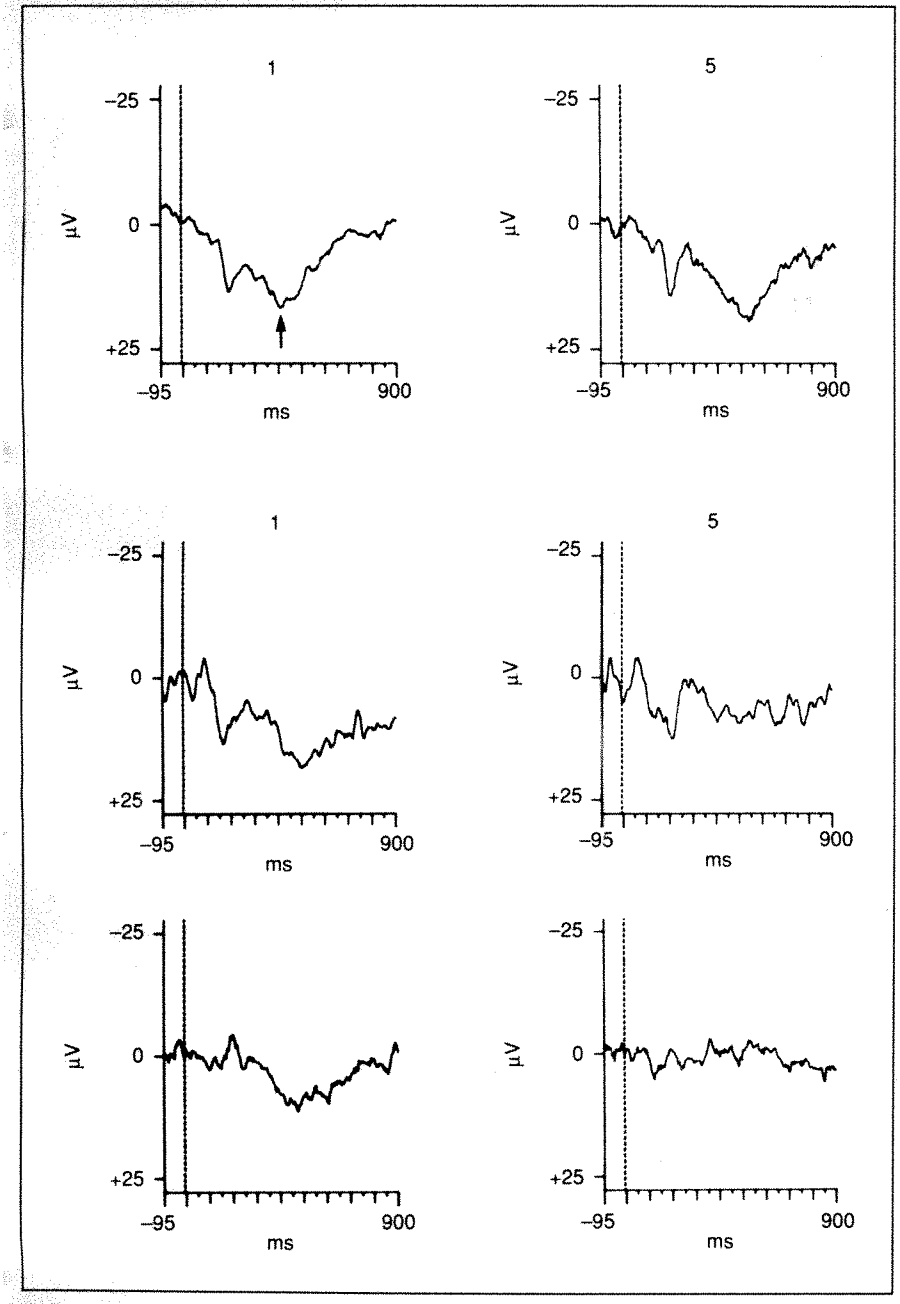

Fig 1.—Averaged event-related potentials (ERPs) elicited by target letters (N = 24). Top, ERPs obtained from an elderly control subject when memory set sizes of one (left) or five (right) letters were used. Center and bottom panels provide a comparison of ERPs obtained from two patients with Alzheimer's disease under the same conditions. Downward deflection indicates positivity at the scalp electrode. The arrow in top left shows the peak of the P300. Note, in particular, that the positive peak at about 200 milliseconds after stimulus onset in the control and the upper of the two patient records is *not* a P300.

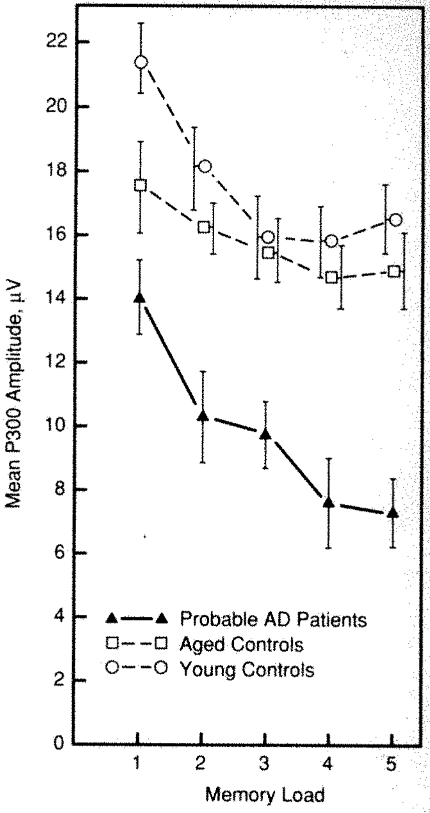

Fig 2.—Mean P300 amplitude to target letters as a function of memory set size in patients with probable Alzheimer's disease (AD), age-matched controls, and young adults. Vertical bars indicate the SEM.

with increasing memory load. An analysis of variance comparing patients with AD with age-matched controls revealed a significant group × memory load interaction ($P<.01$). Further comparisons indicated a difference in reaction time between the two groups with a memory load of five letters. This large increase in reaction time with increasing memory load in patients with AD compared with age-matched controls is indicative of a longer search of temporarily stored information and provides a quantitative behavioral measure of memory dysfunction.

The other behavioral measure, choice accuracy to target letters (Fig 5), showed results similar to reaction time, although in this case, differences between patients with probable AD and elderly controls were less dramatic. Even though an analysis of variance on choice accuracy to target letters revealed a significant group × memory load interaction ($P<.02$), indicating that patients were less accurate with increasing memory load, individual comparisons for each load did not reach significance when probabilities were corrected for the number of *t* tests performed.

COMMENT

Compared with aged individuals, patients with probable AD showed a marked diminution in the amplitude of the P300 component of ERPs recorded during a modified Sternberg memory scanning task *only* when increasing degrees of demand or stress were imposed on mnemonic function. As in the case of a "cardiac stress test," the term *stress* is used herein to refer to a load or demand on the particular system involved. Although patients with AD did not differ from age-matched controls when one item had to be remembered, their P300 potential was significantly reduced in amplitude with increasing memory load. Aged controls did not differ from young adults on this measure. P300 latency, on the other hand, did not differ-

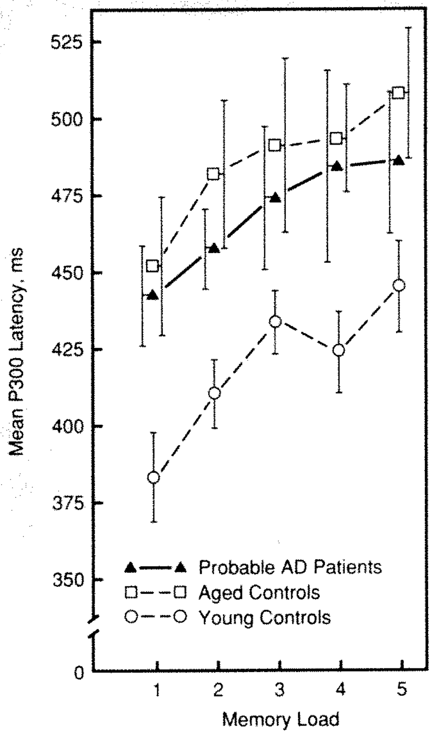

Fig 3.—Mean P300 latency to target letters as a function of memory set size in patients with probable Alzheimer's disease (AD), age-matched controls, and young adults. Vertical bars indicate the SEM.

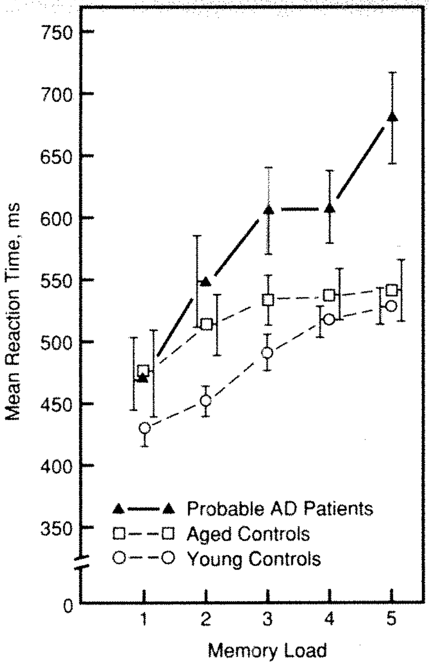

Fig 4.—Mean reaction time to target letters as a function of memory set size in patients with probable Alzheimer's disease (AD), age-matched controls, and young adults. Vertical bars indicate the SEM.

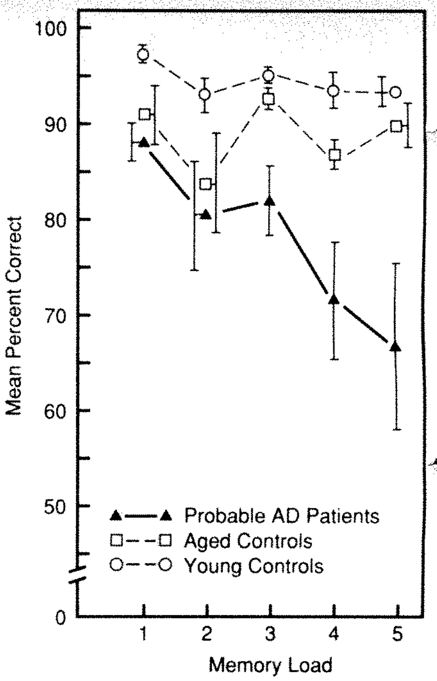

Fig 5.—Mean choice accuracy to target letters as a function of memory set size in patients with probable Alzheimer's disease (AD), age-matched controls, and young adults. Vertical bars indicate the SEM.

entiate patients with AD from age-matched controls, although both showed delayed potentials compared with young adults. The lack of a significant increase in P300 latency in patients with AD compared with aged controls in our study is not surprising given that patients with AD consisted of individuals with mild dementia who were in the early stages of the disease. As indicated in the introduction, Polich et al[20] have demonstrated that an increase in P300 latency is not a sensitive index of memory dysfunction in the early stages of dementing illnesses.

In the present study, the loss or diminution of the P300 potential under conditions of mnemonic stress seemed to provide a more sensitive marker of the dysfunction in the patient population than either behavioral measure recorded during the task. More specifically, the patients with probable AD differed significantly from age-matched controls in P300 amplitude even with a minimal memory load of two letters, while a much greater load was needed before differences in behavioral measures could be detected.

The excessive diminution of P300 amplitude with increasing memory load in the patient population does not seem to be a function of a marked reduction in accuracy. For example, the patient with probable AD whose ERPs are plotted in the bottom tracing of Fig 1 was performing at 80% accuracy with a memory load of five letters, and yet, among the patients with AD, his P300 showed the greatest reduction in amplitude with increasing memory load.

We also reexamined ERP data for some of the patients with probable AD by averaging trials on which they made accurate choices separately from error trials. The ERP data for correct "target" trials were very similar to those described above for all target trials. In addition, we recently tested a patient with dementia due to vascular causes whose choice accuracy was much worse than that of any of the patients with AD included in this study; his P300 potentials, however, were very comparable to those of age-matched controls even with a memory load of five letters. This case provides an excellent example of the dissociation between behavioral (as indicated by choice accuracy) and electrophysiologic findings.

It should also be pointed out that although our task was visual in nature, the results we report cannot be accounted for by possible abnormalities in the peripheral visual system in patients with probable AD.[34] First of all, such peripheral visual system abnormalities would be expected to affect latency measures far more than amplitude measures. Second, in our experiment, following the study period for a given memory set size, all testing was carried out with single-letter presentations. The only variable that differed from trial block to trial block was the number of letters a subject had to remember. Since the task was visual in nature under all conditions, possible peripheral visual abnormalities would have played an equal role in the case of testing with a memory set size of one letter, as well as with four or five letters. Yet, as indicated above, patients with probable AD did not differ from age-matched controls in P300 amplitude when a memory set size of one letter was required.

The occurrence or nonoccurrence of a P300 potential in an individual is not, in itself, a useful marker of memory dysfunction or of a disease process. Lack of this so-called cognitive ERP may be observed in various populations and may result from failure to cooperate with the test, inattention, etc. However, when the P300 is well formed with a minimal memory load and comparable in amplitude to that of controls, but is markedly diminished in amplitude or lost as the memory load increases, patients, in a sense, provide their own controls. Used in the manner described in this article, the modified Sternberg paradigm provides a "stress test" of the integrity of the neural circuitry on which the registration of new experience depends. That circuitry is likely to include the hippocampal formation.

The hippocampal formation is a structure critically involved in the registration of many forms of newly acquired information.[35,36] There is now a substantial body of work indicating that the P300 potential may be generated in or near the hippocampus,[37-40] although it is still not certain that the scalp-recorded P300 has the same origin as that event of similar latency derived from indwelling electrodes in limbic cortex. Nevertheless, it seems likely that the P300 generated in the context of a recent memory task, which is probably dependent on the hippocampus for its accurate performance, reflects the action of hippocampal neurons. Although the correctness of this assumption is not crucial for our conclusion, it is of interest that a direct relationship between hippocampal cell loss or pathology and P300 abnormalities has been found in two recent studies of epileptic patients.[39,41]

Hippocampal pathology or disconnection has been amply demonstrated in AD and is thought to be responsible for the memory impairment associated with the early stages of the disorder.[42-46] We suggest that the recording of ERPs in the context of the Sternberg paradigm, as modified in our hands, may prove to be especially sensitive for the detection of hippocampal abnormalities. Since disturbance in the acquisition of new information is one of the hallmarks of probable AD, the P300 test described herein may provide a sensitive, noninvasive, diagnostic tool or marker during the very early stages of the disease.

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References

1. Sutton S, Braren M, Zubin J, John ER. Evoked potential correlates of stimulus uncertainty. *Science*. 1965;150:1187-1188.

2. Donchin E, Ritter W, McCallum C. Cognitive psychophysiology: the endogenous components of the ERP. In: Callaway E, Tueting P, Koslow S, eds. *Event-Related Brain Potentials in Man*. Orlando, Fla: Academic Press Inc; 1978:349-411.

3. Donchin E, Karis D, Bashore T, Coles MGH, Gratton G. Cognitive psychophysiology and human information processing. In: Coles MGH, Donchin E, Porges SW, eds. *Psychophysiology: Systems, Processes, and Applications*. New York, NY: Guilford Press; 1986:244-267.

4. Duncan-Johnson C. P300 latency: a new metric of information processing. *Psychophysiology*. 1981;18:207-215.

5. Duncan-Johnson C, Donchin E. The P300 component of the event-related brain potential as an index of information processing. *Biol Psychol*. 1982;14:1-52.

6. Fabiani M, Karis D, Donchin E. Effects of strategy manipulation on P300 amplitude in a von Restorff paradigm. *Psychophysiology*. 1985;22:588-589.

7. Fabiani M, Karis D, Donchin E. P300 and recall in an incidental memory paradigm. *Psychophysiology*. 1986;23:298-308.

8. McCarthy G, Donchin E. A metric for thought: a comparison of P300 latency and reaction time. *Science*. 1981;211:77-80.

9. Duncan-Johnson C, Donchin E. On quantifying surprise: the variation of event-related potentials with subjective probability. *Psychophysiology*. 1977;14:456-467.

10. Donchin E, Miller GA, Farwell LA. The endogenous components of the event-related potential: a diagnostic tool. *Prog Brain Res*. 1986;70:87-102.

11. Ford JM, Roth WT, Mohs RC, Hopkins WF, Koppell BS. Event-related potentials recorded from young and old adults during a memory retrieval task. *Electroencephalogr Clin Neurophysiol*. 1979;47:450-459.

12. Ford JM, Pfefferbaum A, Kopell BS. Effects of perceptual and cognitive difficulty on P3 and RT in young and old adults. *Electroencephalogr Clin Neurophysiol*. 1982;54:188-197.

13. Ford JM, Pfefferbaum A. Age-related changes in event-related potentials. *Adv Psychophysiol*. 1985;1:301-339.

14. Goodin DS, Squires KC, Starr A. Long latency event-related components of the auditory evoked potential in dementia. *Brain*. 1978;101:635-648.

15. Marsh GR. Age differences in evoked potential correlates of a memory scanning process. *Exp Aging Res*. 1975;1:3-16.

16. Goodin DS, Aminoff MJ. Electrophysiological differences between demented and nondemented patients with Parkinson's disease. *Ann Neurol*. 1987;21:90-94.

17. Gordon E, Kraiuhin C, Harris R, Meares R, Howson A. The differential diagnosis of dementia using P300 latency. *Biol Psychiatry*. 1986;21:1123-1132.

18. Kraiuhin C, Gordon E, Meares R, Howson A. Psychometrics and event-related potentials in the diagnosis of dementia. *J Gerontol*. 1986;41:154-162.

19. Pfefferbaum A, Wenegrat BG, Ford JM, Roth WT, Kopell BS. Clinical application of the P3 component of event-related potentials, II: dementia, depression and schizophrenia. *Electroencephalogr Clin Neurophysiol*. 1984;59:104-124.

20. Polich J, Howard L, Starr A. Effects of age on the P300 component of the event-related potential from auditory stimuli: peak definition, variation and measurement. *J Gerontol*. 1985;40:721-726.

21. Patterson JV, Michalewski HJ, Starr A. Latency variability of the components of auditory event-related potentials to infrequent stimuli in aging, Alzheimer-type dementia, and depression. *Electroencephalogr Clin Neurophysiol*. 1988;71:450-460.

22. deToledo-Morrell L, Evers S, Hoeppner TJ, Morrell F, Garron DC. A stress test for memory: differential effects of memory load on the amplitude of event-related potentials in aging and Alzheimer's disease. *Soc Neurosci Abstr*. 1988;14:10223.

23. Erickson R. Use of semantic P300 in early Alzheimer's disease detection. *Soc Neurosci Abstr*. 1988;14:102.

24. Gordon E, Kraiuhin C, Zurynski Y, Howson A, Meares R. The P300 event related potential and regional cerebral blood flow in the assessment of patients with disorders of short term memory. *Soc Neurosci Abstract*. 1988;14:102.

25. Meador KJ, Hammond RT, Loring DW, Allen M, Bowers D, Heilman KM. Cognitive evoked potentials and disorders of recent memory. *Neurology*. 1987;37:526-529.

26. Starr A, Barrett G. Disordered auditory short-term memory in man and event-related potentials. *Brain*. 1987;110:935-959.

27. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.

28. Folstein MF, Folstein SE, McHugh PR. 'Mini Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.

29. Mattis S. *Dementia Rating Scale Professional Manual*. Odessa, Fla: Psychological Assessment Resources; 1988.

30. Sternberg S. High-speed scanning of human memory. *Science*. 1966;153:652-654.

31. Jasper HH. The ten-twenty electrode system of the International Federation. *Electroencephalogr Clin Neurophysiol*. 1958;10:371-375.

32. Greenhouse SW, Geisser S. On methods in the analysis of profile data. *Psychometrica*. 1959;24:95-112.

33. deToledo-Morrell L, Morrell F, Hoeppner TJ, Fortney R, Bennett D. Electrophysiological markers of the early stages of Alzheimer's disease. In: Hartmann A, Kuschinsky W, Hoyer S, eds. *Cerebral Ischemia and Dementia*. Heidelberg, Germany: Springer-Verlag. In press.

34. Pollock VE, Schneider LS, Chui HC, Henderson V, Zemansky M, Sloane RB. Visual evoked potentials in dementia: a meta-analysis and empirical study of Alzheimer's disease patients. *Biol Psychiatry*. 1989;25:1003-1013.

35. Milner B. Clues to the cerebral organization of memory. In: Bouser PA, Rougel-Bouser A, eds. *Symposium on Cerebral Correlates of Conscious Experience*. Amsterdam, the Netherlands: Elsevier Science Publishers; 1978:139-153.

36. Zola-Morgan S, Squire LR, Amaral DG. Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J Neurosci*. 1986;6:2950-2967.

37. Halgren E, Stapleton JM, Smith M, Alfafullah I. Generators of the human scalp P3(s). In: Cracco RQ, Bodis-Wollner I, eds. *Evoked Potentials: Frontiers in Clinical Neuroscience*. New York, NY: Alan R Liss Inc; 1986;3:269-284.

38. McCarthy G, Wood CC, Williamson PD, Spencer DD. Task- dependent field potentials in human hippocampal formation. *J Neurosci*. 1989;9:4253-4268.

39. Puce A, Kalnins RM, Berkovic SF, Donnan GA, Bladin PF. Limbic P3 potentials, seizure location and surgical pathology in temporal lobe epilepsy. *Ann Neurol*. 1989;26:377-385.

40. Squires NK, Halgren E, Wilson CL, Crandall PH. Human endogenous limbic potentials: cross-modality and depth surface comparisons in epileptic subjects. In: Gaillard AWK, Ritter W, eds. *Tutorials in ERP Research: Endogenous Components*. Amsterdam, the Netherlands: Elsevier Science Publishers; 1981:217-232.

41. Wood CC, McCarthy G, Kim JH, Spencer DD, Williamson PD. Abnormalities in temporal lobe event-related potentials predict hippocampal cell loss in temporal lobe epilepsy. *Soc Neurosci Abstr*. 1988;14:5.

42. Ball MJ. Neuronal loss, neurofibrillary tangles and granulovascular degeneration in the hippocampus with ageing and dementia: a quantitative study. *Acta Neuropathol*. 1977;37:111-118.

43. Ball MJ, Hachinski V, Fox A, et al. A new definition of Alzheimer's disease: a hippocampal dementia. *Lancet*. 1985;1:14-16.

44. Hamos JE, DeGennaro LJ, Drachman DA. Synaptic loss in Alzheimer's disease and other dementias. *Neurology*. 1989;39:355-361.

45. Hyman BT, Van Hoesen GW, Damasio AR, Barnes CL. Alzheimer's disease: cell specific pathology isolates the hippocampal formation. *Science*. 1984;222:1168-1170.

46. Terry RD, Davies P. Dementia of the Alzheimer type. *Annu Rev Neurosci*. 1980;3:77-95.

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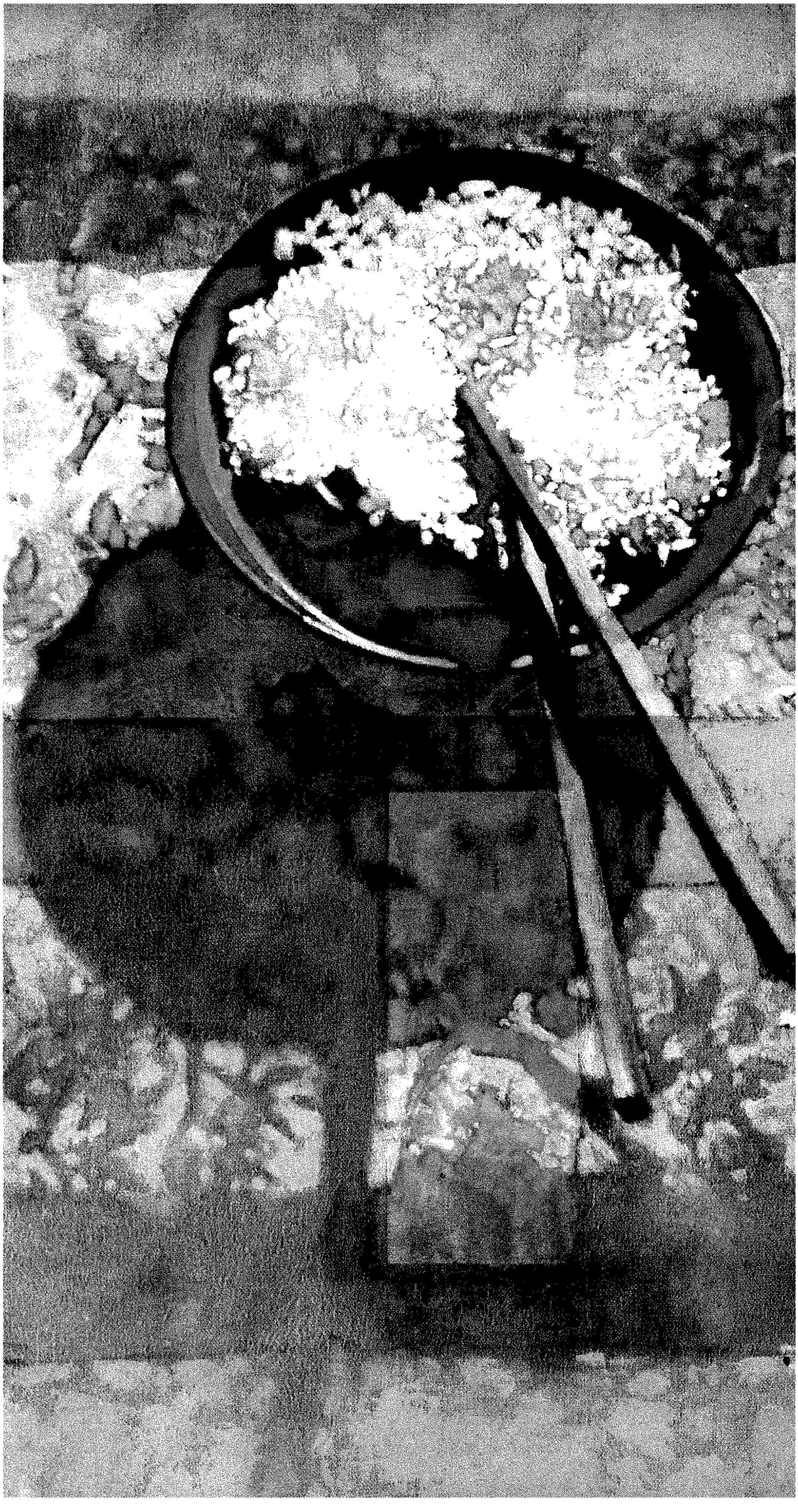

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ergotamine tartrate USP .... 1 mg
caffeine USP .... 100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

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ergotamine tartrate USP .... 2 mg
caffeine USP .... 100 mg

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CONTRAINDICATIONS: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

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Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

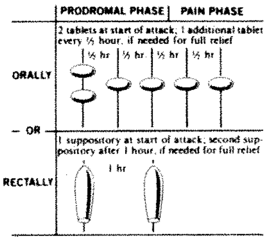
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
ORALLY
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief
½ hr
½ hr
½ hr
½ hr
— OR —
RECTALLY
1 suppository at start of attack; second suppository after 1 hour, if needed for full relief
1 hr

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE: The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

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Shell pink colored, sugar coated, imprinted "CAFERGOT" on one side, "⚠" on other side. Bottles of 250, NDC 0078-0034-28, and cartons of three SigPak® (dispensing unit) packages, each containing 30 tablets in individual blisters, NDC 0078-0034-42.

Cafergot® (ergotamine tartrate and caffeine) Suppositories

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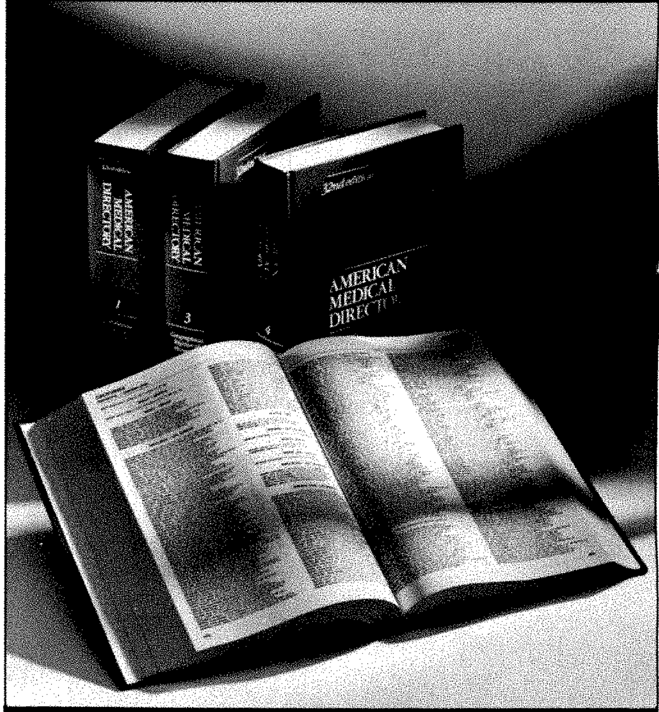
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Retrospective Postmortem Dementia Assessment

Validation of a New Clinical Interview to Assist Neuropathologic Study

Paula B. Davis, MD; Heidi White, MD; Joseph L. Price, PhD; Daniel McKeel, MD; Lee N. Robins, PhD

• Neuropathologic studies of dementia and normal aging suffer from a lack of individuals examined for the presence and severity of dementia before death. To increase clinical information in such cases, a retrospective collateral interview was developed. Thirty-nine individuals were studied; 27 had autopsies. In all cases, the autopsy confirmed the Retrospective Collateral Dementia Interview (RCDI) diagnosis of the presence or absence of dementia; the RCDI had a sensitivity of 88% and a specificity of 80% for specifically detecting probable Alzheimer's disease. Agreement between the RCDI and premortem diagnosis was 96%; between RCDI and medical records, 100%. Agreement between RCDI staging of dementia severity and the last assessment of the living subject was 70%; between the RCDI and a brief staging at death, 86%. This validation confirms the value of postmortem interviews with close informants to assess dementia presence and severity.

(*Arch Neurol.* 1991;48:613-617)

Neuropathologic findings of appropriate numbers and distribution of neurofibrillary tangles and senile plaques[1] remain the gold standard for the diagnosis of senile dementia of the Alzheimer type (SDAT). To understand the spectrum of disease, brain tissue from persons of a broad range of ages and disease severity, including nondemented persons, is highly desirable. Clinicopathologic studies of SDAT and normal aging, however, are plagued by a lack of individuals who are examined for the clinical presence and severity of dementia before death. Even in longitudinal studies of healthy aging and senile dementia, few individuals come to autopsy at a young age or in very mild or moderate stages of dementia. Further, as dementia progresses, it is more difficult for subjects in longitudinal studies to be examined for revised staging of their dementia severity.

In the living subject, the most common source of information about a cognitively impaired person is an interview with an informant, someone who is aware of the person's cognitive and functional abilities or impairment.[2,3] The same resource is often available after death. The psychiatric literature supports the value of such collateral-source information after death in the case of suicide.[4-6] A carefully constructed instrument to interview a knowledgeable collateral source has been shown to be useful and reliable.[4]

Kukull and Larson[7] used a mailed questionnaire to elicit collateral-source information after death to establish a diagnosis of primary degenerative dementia. While highly sensitive, the questionnaire had low specificity. We have devised a collateral-source interview to be used specifically after death. This article presents our study of this interview's validity in making a diagnosis of the presence or absence of dementia, a differential diagnosis of SDAT, and a staging of dementia severity.

PATIENTS AND METHODS

The Retrospective Collateral Dementia Interview (RCDI) is a retrospective, structured telephone interview, conducted with a knowledgeable collateral source, that takes approximately 40 minutes. It was adapted from the Informant Interview given in the Adult Lifestyle and Function Study (1986 and 1987; L. N. Robins, MD, R. F. Fischbach, MD, and P.B.D.), a follow-up study conducted in St Louis, Mo, of elderly participants in the Epidemiologic Catchment Area Study (1981 and 1982) conducted in five sites (including St Louis) by the National Institute of Mental Health, Bethesda, Md.[8,9] The interview includes questions about the relationship between the collateral source and the subject (eg, family or friend and frequency of contact), the circumstances of the subject's death, basic sociodemographic information, and family history of memory disorders. It further asks about aphasia (problems with speech and writing); medical conditions, especially those pertinent to memory (eg, depression, Parkinson's disease, stroke, and seizure disorder); and other factors that can affect cognition (eg, hearing and vision disorders and alcohol and medication use). It also queries the expression of the dementing illness, such as behavioral problems and changes in personality and judgment.

Regarding memory and orientation, questions are posed to elicit the onset, course, and nature of the problems, ie, recent and/or remote memory (by specific items) and orientation to person, place, and time (by specific items). The RCDI includes questions operationalizing the Blessed Dementia Scale items[3] and the Activities of Daily Living scale of Katz et al.[10] These questions are not presented in order as a single set but, rather, are distributed throughout the interview. Thus,

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Presented as a poster exhibit at the American Geriatrics Society Meeting, Boston, Mass, May 12-13, 1989.

Reprint requests to Section of Geriatrics, University of Pittsburgh, B-45 Lothrop Hall, 190 Lothrop St, Pittsburgh, PA 15213 (Dr Davis).

Table 1.—Demographic Characteristics of Postmortem Sample (N = 39)

Age, y (No. of subjects)
54-64 (6)
65-74 (5)
75-84 (21)
85-95 (7)
Mean age, 76.4
Education, y*
Mean schooling, 11.7
Range, 8-16
Gender
M, 17
F, 22

*Information was missing in 18 cases.

Table 2.—Comparison of Retrospective Collateral Dementia Interview (RCDI) Diagnoses With Neuropathologic Autopsy Diagnoses

Is Dementia Present? (N = 27)

		Neuropathologic Autopsy for Dementia	
		Present	**Absent**
RCDI diagnosis for dementia	Present	21	0
	Absent	0	6
Sensitivity, %, 100			
Specificity, %, 100			
Prevalence, %, 78			
Positive predictive value, 1			
Negative predictive value, 1			

When Present, What Type Is the Dementia? (N = 21)

		Autopsy Diagnosis	
		Pure AD	**Other Dementia**
Clinical Diagnosis (RCDI) for Alzheimer's disease (AD)	Probable	14	1
	Possible	2	4
Sensitivity for pure AD, %, 88			
Specificity for pure AD, %, 80			
Prevalence, %, 76			
Positive predictive value, .93			
Negative predictive value, .67			

the clinician is unaware of the subject's score on the Blessed Dementia Scale during assessment and assignment of severity staging. The RCDI was given by either a physician trained and experienced in dementia evaluation or a senior medical student trained in its administration. (The interview was conducted in one case as a written questionnaire at the request of the collateral source.) Interviews conducted by the student were reviewed with the physician, who assigned a diagnosis and severity rating. The interviewer was blinded to all other information regarding the patient when giving and scoring the interview.

Information obtained in the interview allowed the clinician to assign diagnoses in accordance with the Work Group Criteria of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), Bethesda, Md, and the Alzheimer's Disease and Related Disorders Association (ADRDA), Chicago, Ill, for probable Alzheimer's disease.[11] Briefly, SDAT was diagnosed when dementia, consisting of memory loss and impairment of other cognitive abilities, began insidiously and followed a gradually progressive course for 6 months or longer in the absence of other disorders that could account for these changes. Possible SDAT was diagnosed when the above criteria were fulfilled, but either the course was atypical or another (or more than one other) contributing disorder was also present. To compare with neuropathologic findings at autopsy, the contributing disorders considered were vascular dementia and Parkinson's disease.[1,12] Subjects who had no intellectual dysfunction were considered cognitively normal.

Diagnoses made solely from the RCDI were compared with (1) diagnoses given by a physician examining the live subject at the Washington University Alzheimer's Disease Research Center (ADRC), St Louis, Mo, using criteria[13] developed earlier but essentially identical to that of NINCDS-ADRDA; (2) medical records; and (3) neuropathologic findings from autopsy. All neuropathologic autopsies were reviewed by a single neuropathologist. Autopsy cases were divided into the following three groups: cognitively normal, pure Alzheimer's disease (AD) (according to Khachaturian's criteria[1]), or other dementias.

Dementia severity was scored using the Clinical Dementia Rating (CDR), a rating scale of the subject's overall dementia severity.[14,15] Six areas of function (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care) are assessed, and an overall rating is assigned according to established rules. The CDR scores are as follows: CDR 0, normal; CDR 0.5, questionable (or very mild) dementia; CDR 1, mild dementia; CDR 2, moderate dementia; and CDR 3, severe dementia. Severity ratings from the RCDI alone were compared with the following: (1) the CDR given at the last assessment of the living subject and (2) the CDR obtained from a brief (10- to 15-minute), semistructured, telephone ADRC Expiration Interview conducted at the time of the subject's death.

The rating of dementia severity from the full RCDI (the CDR) was also compared with the summary score of the Blessed Dementia Scale[3] items embedded within the RCDI. The full Blessed Dementia Scale is scored with a range of 0 (normal) to 28 (severely impaired); while all items were included in the RCDI, the scores of 0.5 were unavailable for four items (could only score 0 or 1); and scores of 1 were unavailable for one item (could only score 0, 2, or 3). The Blessed Dementia Scale consists of the following two subtests: the Blessed Dementia Scale–Cognitive, scored 0 (normal) to 17 (severely impaired); and the Blessed Dementia Scale–Personality, Interests, and Drives, ranging from 0 (normal) to 11 (severely impaired). In a previous study of living subjects in the Memory and Aging Project and the ADRC of Washington University, subjects' scores on the Blessed Dementia Scale and Blessed Dementia Scale–Cognitive were highly correlated with their CDR scores (0.79 and 0.84, respectively).[16]

After explaining the nature of the study and obtaining consent, collateral sources of the following subjects participated: 23 ADRC subjects who died from July 1986 through January 1989, four persons who donated their bodies to the Washington University School of Medicine, and 12 persons from the general autopsy service. Collateral sources were spouses (17 individuals), adult daughters (14 individuals), adult sons (three individuals), siblings (three individuals), daughter-in-law (one individual), and a nonrelative (one individual). The mean time from death until the interview was conducted was 8 months (range, 2 to 21 months). Demographic characteristics of the subjects studied are presented in Table 1.

Brains were available from 18 of 23 ADRC subjects, two of four participants in the body-donation program, and seven of 12 individuals who underwent general autopsies. All 23 ADRC subjects had a diagnosis and severity staging obtained in life; 21 of these 23 subjects had a restaging of dementia severity from the brief ADRC Expiration Interview at death. Medical records were available in all but one case; that person had a neuropathologic autopsy, however.

RESULTS

Diagnosing Dementia

Six subjects diagnosed by the RCDI as cognitively normal had autopsies, and all were confirmed to be cognitively normal (Tables 2 and 3). Twenty-one subjects diagnosed by the RCDI as having SDAT alone or with another dementing illness underwent autopsies, and all were confirmed to have SDAT. Further, 15 of these subjects were considered to have probable SDAT from the interview—14 of these subjects were confirmed as pure AD neuropathologically, and the last had mixed de-

Table 3.—Diagnoses and Severity Ratings

Case No.	RCDI Diagnosis*	Neuropathologic Diagnosis†	Premortem CDR‡	Expiration CDR	RCDI CDR
1	CN	CN	0	0	0
2	CN	CN	0	0	0
3	CN	CN	...	...	0
4	CN	CN	...	...	0
5	CN	CN	...	...	0
6	CN	CN	...	...	0
7	AD	AD	0	0	0.5
8	AD	AD	...	...	1
9	AD	AD	2	2	2
10	AD	AD	3	3	3
11	AD	AD	1	3	3
12	AD	AD	3	3	3
13	AD	AD	3	3	3
14	AD	AD	3	3	3
15	AD	AD	3	3	3
16	AD	AD	2	2	3
17	AD	AD	3	3	3
18	AD	AD	3	3	3
19	AD	AD	1	...	3
20	AD	AD	3	3	3
21	AD	Other: AD + Vascular (Binswanger's disease)	...	...	3
22	PAD: AD + PD	Other: AD + PD	...	...	3
23	PAD: AD + PD	Other: AD + PD	2	...	3
24	PAD: atypical AD, early aphasia	Other: atypical AD (Pick-Alzheimer spectrum)	...	...	3
25	PAD: AD + vascular	Other: AD + vascular	3	3	3
26	PAD: AD + vascular	AD	3	3	3
27	PAD: AD + PD	AD	...	...	3
28	CN	...	0	0	0
29§	CN	...	...	...	0
30§	CN	...	...	...	0
31§	CN	...	...	...	0
32§	CN	...	...	...	0
33§	CN	...	...	...	0
34§	CN	...	...	...	0
35	AD	...	2	2	2
36	AD	...	2	3	3
37	AD	...	0.5	1	3
38§	PAD: atypical AD, early aphasia	...	...	...	3
39	Vascular dementia	...	3	3	3

*Diagnoses from Retrospective Collateral Dementia Interview (RCDI): CN indicates cognitively normal; AD, probable Alzheimer's disease; PAD, possible Alzheimer's disease; and PD, Parkinson's disease.

†Diagnoses from neuropathologic autopsy; CN indicates cognitively normal; AD, pure Alzheimer's disease; and other, AD and other illness(es).

‡CDR indicates Clinical Dementia Rating; CDR scores as follows: 0, no dementia; 0.5, questionable dementia; 1, mild dementia; 2, moderate dementia; and 3, severe dementia.

§No premortem assessment available; medical records confirmed cognitively normal for cases 29 through 34 and confirmed possible AD for case 38.

mentia, vascular and AD, at autopsy. Of six cases diagnosed by the RCDI as possible SDAT, four were confirmed as atypical AD or as having another dementing disorder in addition to AD. The other two cases had only AD at autopsy. Thus, the RCDI had 100% sensitivity and specificity for detecting the presence or absence of dementia and had 88% sensitivity and 80% specificity for detecting pure AD from mixed dementias that included AD.

We next compared diagnoses from the RCDI with those made when the subject was alive (23 subjects). Three subjects were diagnosed as cognitively normal both by the RCDI and the last premortem clinical assessment. One subject was diagnosed as having probable AD by the RCDI; she was considered cognitively normal at the last clinical assessment. Of the other 15 subjects diagnosed by the RCDI as having probable SDAT, premortem assessment agreed with the RCDI assessment in all cases. Three subjects were diagnosed by the RCDI as having possible SDAT. Two of these three individuals had been considered to have possible AD at their last premortem clinical assessment and one had probable AD. One subject had vascular dementia by both the RCDI and the clinical assessment.

Diagnoses from the RCDI were confirmed by review of medical records, given their limitations.[17] Thus, by comparison with all available standards the RCDI always detected dementia if present and always detected normal cognitive function (case 7 had been considered normal at the last clinical assessment, was diagnosed as probable AD by the RCDI, and was confirmed as pure AD by autopsy). The RCDI misclassified two cases of AD as possible AD, and one case of mixed dementia as pure AD.

Determining the Severity of Dementia

The RCDI also performed well at staging dementia severity. There was 70% agreement between the CDR from the RCDI and the CDR from the last premortem clinical assessment, and 86% agreement between the RCDI-generated CDR and the ADRC Expiration Interview CDR (Table 3). Increasing the time from the last clinical assessment to death had little effect on the agreement of the retrospective interview with premortem staging of severity (Table 4); neither did more elapsed time lessen agreement between the RCDI and the ADRC Expiration Interview. Differences between the retrospective interview staging and premortem staging by CDR category were noted, with less agreement seen for the CDR scores of 0.5, 1, and 2 than for the CDR scores of 0 or 3. The three cases showing discrepancies in staging between the RCDI and the ADRC Expiration Interview all were rated as more severely affected by the RCDI. Older subjects were no more difficult to assess than were younger subjects, although most cases fell into one age category (75 to 84 years).

We also compared the global CDR derived from the RCDI with the rating from the embedded Blessed Dementia Scale[3] items. Using the full Blessed Dementia Scale or the Blessed Dementia Scale–Cognitive, good correlation between the briefer tests and the global CDR was established (0.71 and 0.74, respectively).

COMMENT

A structured, retrospective telephone interview with a knowledgeable collateral source conducted after a subject's death provides both a valid identification of dementia and a diagnosis of SDAT. These findings make the retro-

Table 4.—Factors Potentially Influencing Retrospective Collateral Dementia Interview Severity Staging

Factor	Subjects With Premortem Assessment (N = 23)	% Agreement*	Factor	Subjects With ADRC Expiration Interview CDR (N = 21)	% Agreement†
Time from last clinical assessment to death, mo			Time from death to RCDI, mo		
≤6	8	63	≤6	7	78
7-12	6	67	7-12	5	83
≥12	8	75	≥12	6	100
CDR from last clinical assessment, score			CDR from ADRC expiration interview, score		
0	4	75	0	4	75
0.5	1	0	0.5	0	. . .
1	2	0	1	1	0
2	5	40	2	3	67
3	11	100	3	13	100
Age, y			Age, y		
58-64	1	0	58-64	1	0
65-74	2	0	65-74	1	100
75-84	17	76	75-84	16	88
85-95	3	100	85-95	3	100

*Percent agreement of retrospective interview Clinical Dementia Rating (CDR) with CDR from last clinical assessment.

†Percent agreement of retrospective interview CDR with CDR from Expiration Interview of the Alzheimer's Disease Research Center (ADRC), Washington University, St Louis, Mo.

spective telephone interview a valuable additional source of clinical information for neuropathologic studies of dementia and normal aging. An interview conducted by either an experienced dementia researcher or a well-trained interviewer, with subsequent review and assignment of the diagnosis by an experienced dementia researcher, yielded both the high sensitivity of Kukull and Larson's[7] mail questionnaire and high specificity. The appropriate classification of all cognitively normal subjects is an exciting finding, suggesting that the RCDI will be very useful in documenting normal cognitive function in subjects (young and old) not clinically assessed before death whose brains are available for neuropathologic study. Case 7, in which the RCDI and premortem assessment disagreed, involved a subject followed up prospectively for 7 years as a healthy control. At the second-to-last clinical assessment, the subject was rated as having questionable or very mild dementia (CDR, 0.5). However, the last assessment before death rated the subject cognitively normal (CDR, 0). The subject died 9 months after her last assessment and had the classic findings of AD on neuropathologic autopsy. The RCDI, which was conducted blinded to the above information, had rated the subject as having questionable or very mild dementia (CDR, 0.5). This suggests that this instrument will be helpful even in well-studied individuals who have not been examined recently.

All cases of dementia were identified, and the differential diagnosis of probable-vs-possible AD had high sensitivity and specificity. The ability of the interview to identify probable AD in samples with a lower AD prevalence, more representative of the population at large (50% to 60%), and the impact of the increased misclassification of mixed cases should be reassessed for its use in other settings. We were limited to very few cases of vascular dementia in our sample because of the recruitment pattern in the ADRC. In this study, case 21, misclassified by the RCDI as probable AD, had neuropathologic findings of Binswanger's type arteriosclerotic leukoencephalopathy[18] in addition to AD. The clinical expression of mixed Binswanger's type leukoencephalopathy and AD is difficult to differentiate from AD.[19] Case 26 was classified as possible AD (AD plus vascular) by the RCDI and pure AD by autopsy; case 27, classified as possible AD (AD plus Parkinson's disease) by the RCDI but which was pure AD by autopsy, was the case in which the informant refused a telephone interview but completed the interview as a mailed questionnnaire. Although the RCDI generally did well, its ability to differentiate pure AD from mixed cases may be enhanced by asking more questions about the extent of impact of reported strokes or Parkinson's disease and about the full course of dementia progression (not just onset and last year).

The RCDI can also detect clinical diagnoses, such as emphysema, alcoholism, cancer, depression, and medication effects, that are not standardly assessed by neuropathologic autopsy but that may contribute to the individual's clinical presentation and modify the course of the individual's disease. Further exploration of additional neuropathologic studies (eg, measuring the extent of involvement of Sommer's sector to assess hypoxia[20] or evaluating the degree of loss of cerebral white matter relative to cortex[21] and neuronal loss in the medial mamillary bodies to assess the chronic toxic effects of alcohol[22]) would be interesting to help sort out the pathophysiologic implications of these other disorders.

The retrospective interview also provides valid staging of dementia severity. We had expected cases with longer intervals between the premortem assessment and death to show greater disparity in severity staging because of progression of the disease. We actually found little effect, probably because most patients were either normal (CRD, 0) or severely demented (CDR, 3) at death.

We also expected to find greater differences in agreement between the retrospective interview staging and premortem staging for cases in CDR categories that were more likely to progress and harder to assess (eg, CDR score of 0.5).[23,24] While we did find less agreement for CDR scores of 0.5, 1, and 2 than for CDR scores of 0 and 3, our sample had few subjects in those categories. As interobserver agreement is greatest for the extremes of normal cognitive function and severe dementia, our sample is more likely to show good agreement because most subjects were in these categories. Whether or not some CDR categories are truly more difficult to assess by retrospective interview will require studying more patients with scores of 0.5, 1, and 2 at death.

We thought differences in accuracy of staging by the age of the subjects might be possible, ie, it might be even harder to discern questionable or mild dementia from "normal aging" in subjects older than 80 years of age than in those who were younger. Older subjects were no more difficult to assess than those who were younger; however, 21 of our 39 subjects were 75 to 84 years old when they died.

One instance of disagreement in staging between the RCDI and the ADRC Expiration Interview is the case discussed above with a CDR score of 0.5 by the RCDI, a diagnosis of probable AD, and confirmation of AD at autopsy, but that was rated cognitively normal (CDR, 0) by both the last premortem assessment and the ADRC Expiration Interview. A subject's CDR rating of 1 (mild dementia) by the ADRC Expiration Interview was rated 3 (severe dementia) by the RCDI; this individual had severe aphasia and hepatic carcinoma that we thought interfered with cognitive function.

Several factors may explain the incomplete agreement of staging from the retrospective interview with that from the ADRC Expiration Interview. When the CDR is assigned at death by ADRC, the 15-minute interview is conducted soon, usually within 1 to 7 days of death, and is usually conducted by the nurse rather than by the physician. As the telephone call also has other purposes than assigning a CDR, the call is usually placed to the spouse or whoever lived with the subject, even if that person was not the collateral source who accompanied the subject to premortem assessments. Open-ended questions provide some information about the immediate circumstances of death. Last, the interviewer knows the CDR assigned at the last clinical assessment.

The RCDI, by contrast, was usually performed after the period of acute grief (≥2 months). This introduces the possibility that the collateral source will have forgotten pertinent information. It was longer (about 40 minutes), fully structured, and done with the person who had served as the collateral source for premortem assessment. The interviewer was blinded to any information about the subject, including prior CDR score. The RCDI gathered more information about other medical illnesses (and medications), which often had also progressed since the last clinical assessment. These earlier minor problems had, at times, progressed to a degree such that we thought these problems also contributed to the subject's impaired cognition.

Comparing results from the RCDI with a well-studied index, the Blessed Dementia Scale and its subtests,[3] also confirmed its good performance in staging dementia severity.

A structured, retrospective interview with a knowledgeable collateral source properly diagnosed the presence or absence of SDAT and staged its severity. Use of the interview in larger samples with greater representation of some categories will be useful. Although this is a structured interview, for this study all interviews were conducted and diagnoses and/or staging were performed by trained researchers in dementia. We are currently modifying it slightly, as described above, to improve its ability to distinguish cases of pure AD from those of a mixed origin. As it appears most useful to use experienced researchers in dementia, incorporation of brief, unstructured segments may enhance diagnostic accuracy in unclear cases. Last, we are developing algorithms for automatic (computerized) scoring for diagnosis and staging, with further study of their validity and accuracy.

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Copies of the interview are available on request.

References

1. Khachaturian Z. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42:1097-1105.
2. Jorm AF, Korten AE. Assessment of cognitive decline in the elderly by informant interview. *Br J Psychiatry.* 1988;152:209-213.
3. Blessed G, Tomlinson BE, Roth M. The association between quantitative measures of dementia and of senile change in the cerebral grey matter of elderly subjects. *Br J Psychiatry.* 1968;114:797-809.
4. Robins E. *The Final Months: A Study of the Lives of 134 Persons Who Committed Suicide.* New York, NY: Oxford University Press; 1981.
5. Shaffer D, Ehrhardt AA, Greenhill L. *The Clinical Guide to Child Psychiatry.* New York, NY: Free Press; 1985.
6. Shneidman ES, Farberow NL, eds. *Clues to Suicide.* New York, NY: Blakiston Division of McGraw-Hill International Book Co; 1957.
7. Kukull WA, Larson EB. Distinguishing Alzheimer's disease from other dementias: questionnaire responses of close relatives and autopsy results. *J Am Geriatr Soc.* 1989;37:521-527.
8. Eaton WW, Holzer CE, VonKorff M, et al. The design of the Epidemiologic Catchment Area Surveys: the control and measurement of error. *Arch Gen Psychiatry.* 1984;41:942-948.
9. Regier DA, Meyers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area Program. *Arch Gen Psychiatry.* 1984;41:934-940.
10. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: the index of ADL: a standardized measure of biological and psychosocial function. *JAMA.* 1963;185:914-919.
11. McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's Disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
12. Tierney MC, Fisher RH, Lewis AJ, et al. The NINCDS-ADRDA Work Group criteria for the clinical diagnosis of probable Alzheimer's disease: a clinicopathologic study of 57 cases. *Neurology.* 1988;38:359-364.
13. Berg L, Hughes CP, Coben LA, et al. Mild senile dementia of the Alzheimer type: research diagnostic criteria, recruitment, and description of a study population. *J Neurol Neurosurg Psychiatry.* 1982;45:962-968.
14. Hughes CP, Berg L, Danziger WL, et al. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566-572.
15. Berg L. The Clinical Dementia Rating (CDR) of Washington University. *Psychopharmacol Bull.* 1988;24:637-639.
16. Davis PB, Morris JC, Grant E. Brief screening tests versus clinical staging in senile dementia of the Alzheimer type. *J Am Geriatr Soc.* 1990;38:129-135.
17. Burnum JF. The misinformation era: the fall of the medical record. *Ann Intern Med.* 1989;110:482-484.
18. Babikian V, Ropper AH. Binswanger's disease: a review. *Stroke.* 1987;18:2-12.
19. Morris JC, McKeel DW, Fulling K, Torack RM, Berg L. Validation of clinical diagnostic criteria for Alzheimer's disease. *Ann Neurol.* 1988;24:17-22.
20. Brierley JB, Adams JH, Graham DI, Simpsom SA. Neocortical death after cardiac arrest. *Lancet.* 1971;2:560-565.
21. de la Monte S. Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch Neurol.* 1988;45:990-992.
22. Mayes AR, Meudell PR, Mann D, Pickering A. Location of lesions in Korsakoff's syndrome: neuropsychological and neuropathological data on two patients. *Cortex.* 1988;24:367-388.
23. Morris JC, Gado M, Torack RM, McKeel DW Jr. Binswanger's disease or artifact: a clinical, neuroimaging, and pathological study of periventricular white matter changes in Alzheimer's disease. *Adv Neurol.* 1990;51:47-52.
24. Rubin EH, Morris JC, Grant EA, et al. Very mild senile dementia of the Alzheimer type, I: clinical assessment. *Arch Neurol.* 1989;46:379-382.

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HP013

Neuropathologic and Neurochemical Correlates of Psychosis in Primary Dementia

George S. Zubenko, MD, PhD; John Moossy, MD; A. Julio Martinez, MD; Gutti Rao, MD;
Diana Claassen, MD; Jules Rosen, MD; Ursula Kopp

• Neuropathologic and neurochemical correlates of psychosis were determined using brain tissue from 27 autopsy-confirmed cases of Alzheimer's disease. The densities of senile plaques and neurofibrillary tangles were determined in the middle frontal and superior temporal cortex, the prosubiculum, and the entorhinal cortex of the hippocampus. The concentrations of norepinephrine, dopamine, and serotonin, the metabolites of these biogenic amines, and the specific activity of choline acetyltransferase were also determined in these four cortical regions as well as in the substantia nigra, thalamus, amygdala, and caudate nucleus. Psychosis was associated with significantly increased densities of senile plaques and neurofibrillary tangles in the prosubiculum and middle frontal cortex, respectively, with trends toward increased densities of these lesions in the other areas examined. This finding is consistent with the increased rate of cognitive decline that accompanies this behavioral disorder. Psychosis was also associated with the relative preservation of norepinephrine in the substantia nigra, with trends in this direction for five of the remaining seven brain regions examined, and a significant reduction of serotonin in the prosubiculum that was accompanied by trends toward reduced levels of serotonin and 5 hydroxyindoleacetic acid in the remaining regions. The profile of neuropathologic and neurochemical changes associated with psychosis is distinct from that previously reported for major depression in the context of primary dementia.

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Psychosis, as defined by the presence of delusions or hallucinations, is a common behavioral complication of primary dementia in the elderly, and in Alzheimer's disease (AD) in particular. In fact, psychosis was present in the original case described by Alzheimer in 1907.[1] Estimates of the prevalence of psychosis in AD obtained from cross-sectional studies of clinically diagnosed patients evaluated in diverse clinical settings have ranged from 10% to 73%, with most estimates in the range of 28% to 38%.[2] In recent prospective, longitudinal studies, psychosis has been reported to emerge in approximately half of the patients with clinically diagnosed[3] or histologically confirmed[4] AD prior to death. Therefore, this behavioral syndrome constitutes an important source of comorbidity in patients with AD.

In addition to its relevance to clinical management, the development of psychosis in the context of AD has prognostic significance. Patients with psychosis exhibit a more rapid cognitive decline,[3-5] but not a higher rate of mortality,[3,4] than patients who do not develop this syndrome. These observations contrast with those for major depression, another common behavioral source of comorbidity in AD, which appears to be accompanied by an increased rate of mortality,[6,7] but not an increased rate of cognitive decline.[8]

The clinical and prognostic distinctions of psychosis and major depression provide evidence that supports the validity of these diagnoses in primary dementia, and also suggests that the neuropathologic and neurochemical determinants of these syndromes may not be identical. Chronic idiopathic psychoses that typically occur earlier in life have been reported to be accompanied by a selective decrease in blood flow[9-12] and decreased glucose metabolism[13-16] in the frontal cortex, and by cell loss and cytoarchitectural abnormalities in the neocortex and hippocampus.[17-22] These findings in such an etiologically heterogeneous group of patients suggests that they may also be relevant to psychoses of later onset, including those associated with neurodegenerative disorders. In contrast, major depression in primary dementia is associated with selective degeneration of aminergic nuclei in the brain stem,[6,7,23] but no increase in the density of senile plaques (SP) or neurofibrillary tangles (NFT) in the cerebral cortex.[6]

Based on these considerations, we performed a clinicopathologic study of psychosis using brain tissue from 27 patients who died with histologically confirmed AD. The densities of SP and NFT were quantified in four cortical regions, and the concentrations of biogenic amines and their metabolites, along with the specific activity of choline acetyltransferase, were determined in eight cortical and subcortical regions.

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Morphologic and neurochemical correlates of psychosis are described and compared with those previously reported for major depression in 37 patients with primary dementia. In our previous study, 30 of 37 patients also met the histologic criteria for AD.[6]

SUBJECTS AND METHODS

Clinical Assessments and Subject Population

Subjects were referred from an ongoing longitudinal study of AD and related dementias. Written informed consent was provided by the patient's legal guardian (usually the next of kin) along with the patient's assent at the time of entry into the study. Written informed consent for autopsy was also provided by the legal guardian at the time of death. The 27 patients (13 males, 14 females) included in this study met consensus clinical criteria for probable or possible AD[24] and the *Diagnostic and Statistical Manual of Mental Disorders-III-Revised* criteria for primary degenerative dementia of the Alzheimer type,[25] as applied by board-certified neurologists and psychiatrists. The clinical and laboratory procedures used to operationalize these diagnostic criteria have been described in detail previously.[4,26-28] All 27 cases also met histopathologic criteria for AD, based on age-specific densities of SP and NFT.[29]

Psychiatric and Neurologic Assessments

Patients received complete psychiatric and neurologic examinations at the time of entry into the study, and these examinations were repeated annually until death. Each psychiatric examination included, but was not limited to, an assessment conducted according to the guidelines of the Initial Evaluation Form, a standardized instrument that specifies and defines the items to be covered, yet allows the clinician the flexibility to adjust to the order of items in the interview to probe for the information required.[30-32] The sections of the form include history of present illness; symptom inventory with specific items related to psychosis and to major depression; family, personal, and social history; physical health history and physical examination; diagnostic formulation; and disposition. Information is solicited from the patient, available caregivers, other informants, and documentary sources. This structured format was designed to cover all psychiatric disorders and has been validated for use in elderly psychiatric patients.[31]

The definition of psychosis in the *Diagnostic and Statistical Manual of Mental Disorders-III-Revised* requires "gross impairment in reality testing and the creation of a new reality."[25] According to this definition, delusions or hallucinations provide "direct evidence" of psychosis, but reasonable inference of a disturbance in reality testing from disorganized behavior may also be used to satisfy this definition. Since disorganized or aberrant behavior in the context of dementia is often attributable to cognitive impairment rather than a disturbance of reality testing, the presence of delusions or hallucinations was required for the diagnosis of psychosis. Delusions and hallucinations were also defined as described in *Diagnostic and Statistical Manual of Mental Disorders-III-Revised.*[25] A delusion was defined as "a false personal belief based on incorrect inference about external reality and firmly sustained in spite of what almost everyone else believes and in spite of what constitutes incontrovertible and obvious proof or evidence to the contrary." Moreover, "the belief is not one ordinarily accepted by other members of the person's culture or subculture." A hallucination is "a sensory perception without external stimulation of the relevant sensory organ." In our assessments, persistent misidentification syndromes were invariably associated with paranoid delusions and therefore did not present a practical problem in establishing the presence of psychosis. Psychotic symptoms that emerged only in the context of delirium were not included. The definition of psychosis employed in this study is similar to that employed in previous studies of psychosis in demented patients.[2-5] Since the *Diagnostic and Statistical Manual of Mental Disorders-III-Revised* is ambiguous about the affective and vegetative symptoms required for establishing the diagnosis of primary degenerative dementia of the Alzheimer type "with depression," the criteria for major depression were employed. The 27 subjects enrolled in our investigation were included in a previously published longitudinal study of the emergence of psychosis and depression in AD.[4]

Neuropathologic Methods

All brains were removed by a neuropathologist as a first procedure for the autopsy as previously described.[6,23,33,34] After weighing the unfixed brain, the brain stem and cerebellum were separated by intercollicular section. The cerebral hemispheres were initially sectioned in the coronal plane at the anterior border of the optic chiasm and the infundibulum of the pituitary. The hemispheres were then sectioned at 1-cm intervals and cooled by ice to retard autolysis. The brain stem and cerebellum were sectioned in the transverse plane at 0.5-cm intervals. Uniform tissue samples for neurochemical studies were obtained from anatomic areas using a pituitary biopsy rongeur and frozen at −70°C until biochemical studies were performed. After sampling for neurochemical studies, the brain sections were fixed flat in buffered 4% formaldehyde solution for at least 2 weeks. Tissue blocks for light microscopy were then obtained from undisturbed sections corresponding as exactly as possible to the areas adjacent to those sampled for neurochemical studies. Following standard tissue processing and paraffin embedding, a general survey was made with hematoxylin-eosin-stained sections, and 8-μm-thick sections stained with the Bielschowsky silver impregnation method were evaluated. Selected sections were also stained with congo red for amyloid and with a combined Nissl-myelin technique, with the Masson trichrome stain, and for glial fibrillary acidic protein.

Morphometry of coded samples was performed by neuropathologists who were unaware of the associated demographic and clinical information. The densities of SP and NFT per magnification field (×200) were determined for the middle frontal and superior temporal cortex, as well as the prosubiculum and entorhinal cortex of the hippocampus, as previously described.[33,34] Estimates of repeated-rater and inter-rater reliability were 0.84 or greater, and have been described in detail elsewhere.[33,34]

Neurochemical Methods

In addition to the four cortical regions subjected to morphometry, neurochemical analysis was performed on tissue obtained from the substantia nigra, thalamus, amygdala, and caudate nucleus. The concentrations of the neurotransmitters norepinephrine (NE), dopamine (DA), and serotonin (5-HT), as well as the NE metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), the dopamine metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in brain tissue were determined by reversed-phase, high-pressure liquid chromatography with electrochemical detection as previously described.[35,36] The sensitivity of this analytic method was in the range of 0.05 to 0.10 pmol for the biogenic amines and their metabolites.

Since MHPG is largely present in conjugated forms in brain tissue, the measurement of this noradrenergic metabolite required an initial hydrolysis step for quantitative recovery.[37] Samples of brain tissue (20- to 40-mg samples) were homogenized in 15 volumes of 1 N acetic acid containing 3,4-dihydroxybenzylamine as an internal standard. After 15 minutes at 4°C, the resulting homogenates were adjusted to pH 4 by the addition of 6 N sodium hydroxide (6 μL/300 μL homogenate), clarified by centrifugation at 30 000 g for 10 minutes at 4°C, and analyzed by reversed-phase high-pressure liquid chromatography.

For the remaining neurochemical determinations, tissue samples were homogenized at 4°C in 9 volumes of 75 mmol/L of phosphate buffer (pH 7.4) containing freshly added 3,4-dihydroxybenzylamine as an internal standard, and aliquots were removed for the measurement of choline acetyltransferase (EC 2.3.1.6) activity. The remainder of each homogenate was immediately acidified to pH 4 by a 1:3 dilution with freshly prepared mobile-phase lacking acetonitrile (100 mmol/L of sodium phosphate, 1 mmol/L of 1-heptanesulfonic acid, and 1 mmol/L of ethylenediaminetetraacetic acid, adjusted to pH 2.9 with saturated citric acid) to ensure the stability of the biogenic amines and their metabolites. Inclusion of the internal standard at the time of homogenization control for any degradation of the biogenic amines that may have occurred during the interval at neutral pH and 4°C. Separate control experiments indicated that less than 10% degradation occurred under these conditions. The resulting suspensions were homogenized again and clarified by centrifugation at 33 000g for 10 minutes at 4°C. The protein concentrations of the pellets were determined by the method of Lowry and coworkers.[38] The supernatants were used directly to determine the tissue concentrations of the neurotransmitters and metabolites, with the exception of NE, which could not be satisfactorily resolved from the solvent front. Instead, NE was adsorbed from an aliquot of each supernatant with alumina and recovered by extraction of the alumina with 0.1 N perchloric acid. The concentration of NE was determined using the resulting perchloric acid extracts. For each brain, the concentrations of these compounds in corresponding regions from the left and right hemispheres were averaged and expressed as picomoles per milligram of protein.

Choline acetyltransferase activity was assayed in tissue homogenates by a minor modification of Fonnum's method,[39] as previously described.[23,34] The 40-μL reaction mixtures contained 20 μL of homogenate and 20 μL of a solution of 600 mmol/L of sodium chloride, 40 mmol/L of magnesium chloride, 2 mmol/L of eserine, 50 mg/dL of bovine serum albumin, 0.73 mmol/L of [acetyltritium]-coenzyme A (5.52 mCi/mmol), and 5 mmol/L of choline iodide in 75 mmol/L of phosphate buffer at pH 7.4. After incubation for 20 minutes at 38°C, the reactions were stopped by immersing the tubes in an ice bath. Labeled acetylcholine in each reaction mixture was extracted into 150 μL of 7.5% tetraphenylboron in 3-heptanone and quantified by scintillation spectrometry. Specific activities were calculated from duplicate assays and the average values from corresponding regions from the left and right hemispheres were expressed as nanomoles of acetylcholine synthesized per hour per milligram of protein.

Statistical Analysis

The sex ratios in the groups of patients with or without psychosis were compared using Fisher's Exact Test. Mean values of the continuous clinical, morphometric, and neurochemical variables were compared using the Mann-Whitney-Wilcoxon rank sum test. Two-tailed tests of significance were employed.

Table 1.—Demographic and Clinical Correlates of Psychosis in 27 Patients With Alzheimer's Disease*

	Psychosis		
	Absent	**Present**	***P***
Present No.	14	13	. . .
Male/female	9/5	4/9	.13
Age at death, y	75.1 ± 7.2	68.8 ± 7.6	.08
Age at onset, y	69.2 ± 7.6	64.4 ± 7.7	.15
Duration of symptoms, y	5.9 ± 2.0	5.5 ± 2.5	.55
Postmortem interval, h	7.1 ± 4.8	7.0 ± 6.7	.34
Brain weight, g	1224 ± 203	1167 ± 127	.25

*Sex ratios were compared with Fisher's Exact Test. Means ± SDs were compared using the Mann-Whitney-Wilcoxon summed ranks test. All tests of significance were two tailed.

Table 2.—Densities of Senile Plaques in 27 AD Patients With or Without Psychosis*

	Psychosis		
	Absent	**Present**	***P***
	Neocortex		
Middle frontal cortex	20.2 ± 15.4	25.5 ± 9.7	.26
Superior temporal cortex	16.3 ± 10.4	20.9 ± 6.3	.13
	Allocortex		
Prosubiculum	5.6 ± 4.3	11.1 ± 5.6	.007†
Entorhinal cortex	11.0 ± 7.3	11.8 ± 4.3	.33

*AD indicates Alzheimer's disease. Means ± SDs were compared using two tailed Mann-Whitney-Wilcoxon summed ranks tests.

†Statistically significant difference.

Table 3.—Densities of Neurofibrillary Tangles in 27 AD Patients With or Without Psychosis*

	Psychosis		
	Absent	**Present**	***P***
	Neocortex		
Middle frontal cortex	4.6 ± 4.5	11.0 ± 8.9	.04†
Superior temporal cortex	9.9 ± 8.4	12.8 ± 10.5	.68
	Allocortex		
Prosubiculum	20.5 ± 14.6	21.2 ± 10.0	.81
Entorhinal cortex	10.8 ± 6.9	13.0 ± 5.0	.53

*NFT indicates neurofibrillary tangles; AD, Alzheimer's disease. Means ± SDs were compared using two tailed Mann-Whitney-Wilcoxon summed ranks tests.

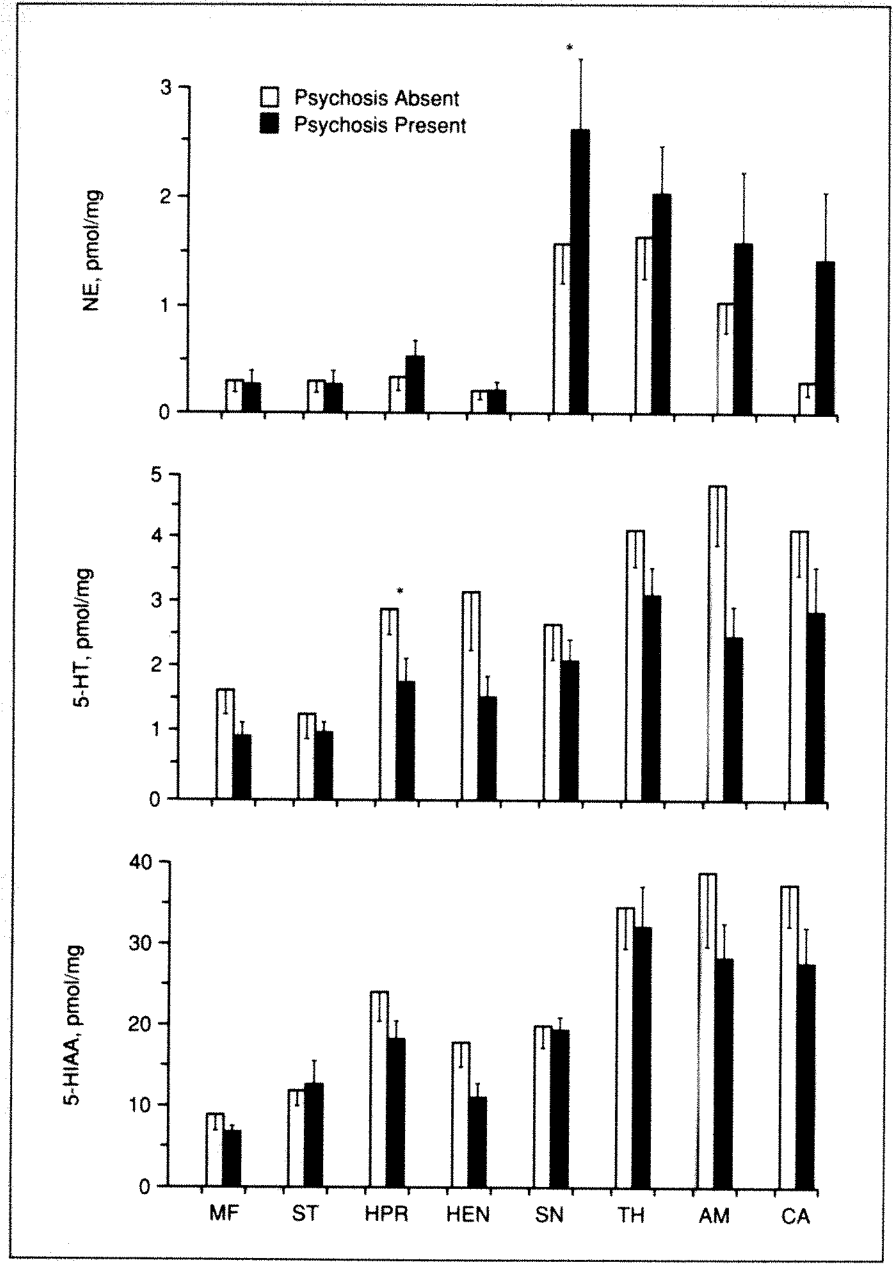
†Statistically significant difference.

RESULTS

All 27 subjects included in the study suffered from histologically confirmed AD, as determined at autopsy. Demographic and clinical characteristics of the study sample are presented in Table 1. Thirteen of the patients (48%) developed psychosis, as defined by the emergence of delusions or hallucinations, between the onset of dementia and death. Psychosis remitted in only two of these 13 cases prior to death. The observed prevalence of psychosis was consistent with previously reported results from other prospective studies of behavioral syndromes in AD.[3,4] Ten of the 27 patients also met criteria for major depression, but were nearly equally distributed between the groups with (n = 6) and without (n = 4) psychosis. As a group, patients who developed psychosis did not differ significantly in sex ratio, mean age at death, mean age at onset of dementia symptoms, mean duration of illness, mean postmortem interval, or mean brain weight, from those who did not develop psychosis.

The relationship of psychosis to the cortical densities of SP and NFT is described in Tables 2 and 3. The development of psychosis was associated with significant increases in the mean densities of SP and NFT in the prosubiculum and middle frontal cortex, respectively. Trends toward increases in the densities of these morphologic lesions were also observed in the other three cortical regions examined.

In addition to the four cortical regions subjected to morphometric analysis, the concentrations of the neurotransmitters NE, DA, and 5-HT, their major metabolites, and the specific activity of choline acetyltransferase were quantified in the substantia nigra, thalamus, amygdala, and caudate nucleus. The results of the brain regional analysis of NE, 5-HT, and 5-HIAA are presented in the Figure. Psychosis was associated with a significantly greater concentration of NE in the substantia nigra that was accompanied by trends in this direction for the three remaining subcortical areas and two of the four cortical regions. The levels of MHPG were determined in the middle frontal and superior temporal cortex, entorhinal cortex, and caudate nucleus, for which adequate brain tissue was available. Psychosis was associated with trends toward



Noradrenergic and serotonergic correlates of psychosis in Alzheimer's disease were examined in the middle frontal (MF) and superior temporal (ST) cortex, prosubiculum (HPR) and entorhinal cortex (HEN) of the hippocampus, substantia nigra (SN), thalamus (TH), amygdala (AM), and caudate nucleus (CA). Mean values are presented as histobars with standard errors. Statistically significant comparisons ($P<.05$) are marked by an asterisk. Metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) concentrations were determined only for the MF, ST, HEN, and CA regions. Respective mean levels of MHPG (±SE) in picograms per milligram were 0.84 ± 0.21, 0.97 ± 0.29, 1.19 ± 0.30, and 0.76 ± 0.15 for patients without psychosis; 0.85 ± 0.30, 1.04 ± 0.28, 1.54 ± 0.41, and 0.86 ± 0.25 for patients with psychosis. 5-HIAA indicates 5-hydroxyindoleacetic acid; 5-HT, serotonin; and NE, norepinephrine.

greater MHPG levels in all four of these regions, no one of which reached statistical significance. The emergence of psychosis was also associated with a statistically significant reduction of 5-HT in the prosubiculum that was accompanied by trends toward reduced levels of 5-HT and its metabolite 5-HIAA in all eight brain regions studied. In contrast to these results, psychosis was not associated with a significant change in the level of DA, its metabolites DOPAC and HVA, or choline acetyltransferase specific activity, in any of the brain regions studied.

Six (43%) of the 14 nonpsychotic patients and 10 (77%) of the 13 psychotic patients were receiving neuroleptic medications (haloperidol, thioridizine, or perphenazine) at the time of death. To assess the effects of neuroleptic medications on the neurochemical variables studied, the cases were stratified by whether or not neuroleptic medications were being administered prior to death and the mean values of these variables were compared. No significant effects of neuroleptic exposure were detected, nor were consistent trends observed. Therefore the psychosis-related alterations in the concentrations of these biogenic amines did not appear to have resulted from neuroleptic exposure.

COMMENT

In our prospective clinicopathologic study of AD, the occurrence of psychosis was associated with increased densities of SP and NFT in the cortex compared with the patients who did not develop psychosis. In AD, the density of SP in the neocortex typically exceeds that found in the allocortex, while the reverse is true for NFT. In this study, the greatest increases in SP and NFT were found in the allocortex and neocortex, respectively, tending to reduce the typical disparities in lesion density between these brain areas. The significance of this finding is unclear, but it is a pattern previously reported to be associated with an earlier age onset of dementia.[40]

The finding that psychosis was associated with significantly greater levels of NE in the substantia nigra, with similar trends in other brain areas, warrants further considerations. Since these values were similar to those observed in brains from elderly control subjects who had no history of neurologic disease prior to death,[23] this finding would seem to have resulted from the relative preservation of NE levels rather than an increase in the levels of their neurotransmitters. This result suggests the existence of a minimum threshold of noradrenergic functioning that is required for the expression of psychosis. Therefore, adrenergic antagonists may have a role in the treatment of certain demented patients with agitated psychosis. We have previously reported a summary of the results of an open trial of propranolol, in which a significant fraction of such patients exhibited clinical improvement.[41]

A comparison of the clinical, neuropathologic, and neurochemical features of psychosis and major depression in the context of primary dementia is presented in Table 4.[3-8,23,42] In our studies of behavioral syndromes in primary dementia, neither patients with psychosis[4] nor those with major depression[6] exhibited an age of onset of dementia that differed significantly from that of patients who did not develop these syndromes. How-

Table 4.—Comparison of Clinical, Neuropathologic, and Neurochemical Correlates of Psychosis and Major Depression in Primary Dementia*

	Psychosis	Major Depression
Sex, age at onset, duration of illness, brain weight	No change[3,4]	No change[6-8,41]
Mortality rate	No change[3,4]	Increased?[6,7]
Rate of cognitive decline	Increased[3-5]	No change[8]
Cortical SP and NFT	Increased SP in HPR and increased NFT in MF; trends toward increases of SP and NFT in remaining areas†	No change[6]
Degeneration of LC and SN	No change[7]	Increased[6]
Norepinephrine	Increased in SN; trends toward increases in five of seven remaining areas†	Decreased in neocortex and allocortex; trends toward decreases in all areas[23]
Serotonin	Reduced in HPR; trends toward decreases in remaining areas†	Trends toward decreases in all areas[23]
Dopamine	No change†	Increased in HPR; no consistent trends in other areas[23]
Choline acetyltransferase activity	No change†	Relative preservation in TH, AM, and CA; trends in same direction for most remaining areas[23]

*Changes are expressed relative to demented patients without the respective behavioral syndrome. Densities of senile plaques (SP) and neurofibrillary tangles (NFT) were determined in the middle frontal (MF) and superior temporal cortex, and the prosubiculum (HPR) and entorhinal cortex (HEN) of the hippocampus. In addition to these areas, neurochemical analysis was performed in the substantia nigra (SN), thalamus (TH), amygdala (AM), and caudate (CA) nucleus. LC indicates locus ceruleus.

†Data cited from our study.

ever, the relationship of these behavioral syndromes to the age at onset of cognitive impairment among demented patients is controversial. One reason for this may lie in the limitations inherent in making retrospective estimates of the age when cognitive decline begins. Moreover, the resolution of this issue is likely to require population-based studies, so that the potential sampling bias favoring the referral of patients whose functioning is disproportionately impaired by behavioral disorders can be avoided.

Several investigations, including two prospective longitudinal studies,[3,4] have found that psychosis is associated with an increased rate of cognitive decline among patients with primary dementia, although the presence of psychosis did not significantly affect the mortality rate. In contrast, major depression does not appear to affect the rate of cognitive decline in patients with clinically diagnosed AD.[8] Instead, two studies have suggested that the emergence of major depression may be associated with an increase in the rate of mortality among patients with primary dementia.[6,7]

Substantial differences also become apparent when comparing the reported neuropathologic and neurochemical correlates of psychosis and major depression in the context of primary dementia. In this study, psychosis was associated with increased neurodegenerative changes in the cortex, but neither the neurochemical evidence presented here, nor previously published morphometric data,[7] found psychosis to be associated with increased degeneration of subcortical aminergic nuclei. In contrast, we previously reported that major depression in primary dementia is associated with increased degeneration of the locus coeruleus and substantia nigra, but not increased numbers of morphologic lesions in the neocortex or allocortex.[6] Furthermore, the profiles of neurochemical changes associated with psychosis and major depression[23] differ considerably, except for the suggestion of modest generalized decrements in 5-HT and 5-HIAA that occur in both behavioral syndromes and may be nonspecifically related to behavioral stress. In summary, the neuropathologic and neurochemical correlates of psychosis and major depression that we describe are selective; each syndrome is associated with distinctive morphometric and neurochemical changes in specific brain regions (Table 4).

The neuropathologic and neurochemical changes associated with psychosis and major depression in primary dementia are probably important determinants of prognoses in these syndromes, as well as the symptoms of the syndromes themselves. Increased densities of SP and NFT in the cerebral cortices of patients with psychosis may be directly related to the increased rate of cognitive decline observed in this subgroup.[3-5] In addition, cortical degeneration itself may render psychosis in primary dementia less likely to undergo spontaneous remission and less responsive to pharmacotherapy than the idiopathic psychoses that typically occur earlier in life. In a prospective longitudinal study of AD, the persistence of psychotic symptoms over time was evident even when neuroleptic drugs were prescribed.[4] However, even increased degenerative cortical changes may not be associated with decreased longevity when the fundamental necessities of life are provided in a supervised nursing care environment, as was the case for the majority of our patients.

Major depression in primary dementia does not appear to be associated with increased degeneration of the cerebral cortex or an increased rate of cognitive decline.[6,8] However, the selective degeneration that occurs in the brain stem may also indicate that other physiologic functions, including swallowing, respiration, and cardiovascular homeostasis, may be affected because other brainstem centers are also involved. In the absence of extracorporeal life support devices, such dysfunctions are likely to increase mortality even when complete custodial care is provided. This hypothesis may also explain the observation that the development of sleep apnea, presumed to be related to dysfunction or degeneration of brain-stem structures, is predictive of increased mortality among elderly patients with idiopathic major depression.[43]

As demonstrated by our studies of major depression[6,23] and psychosis, the presence of behavioral syndromes may have significant effects on measures of morphologic and neurochemical pathology in degenerative brain disease. We therefore recommend that clinical descriptions of patients employed in such studies include assessments of psychiatric syndromes and that study designs control for the potential effects of these disorders.

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References

1. Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. *Allemmeine Zeitschr Psychiatr Psychisch-Gericht Med.* 1907;64:146-148.

2. Wragg RE, Jeste DV. Overview of depression and psychosis in Alzheimer's disease. *Am J Psychiatry.* 1989;146:577-587.

3. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. *Biol Psychiatry.* 1989;25:39-48.

4. Rosen J, Zubenko GS. Emergence of psychosis and depression in the longitudinal evaluation of Alzheimer's disease. *Biol Psychiatry.* 1991;29:224-232.

5. Stern Y, Mayeux R, Sano M, Hauser WA, Bush T. Predictors of disease course in patients with probable Alzheimer's disease. *Neurology.* 1987;37:1649-1653.

6. Zubenko GS, Moossy J. Major depression in primary dementia: clinical and neuropathologic correlates. *Arch Neurol.* 1988;45:1182-1186.

7. Zweig RM, Ross CA, Hedreen JC, et al. The neuropathology of aminergic nuclei in Alzheimer's disease. *Ann Neurol.* 1988;24:233-242.

8. Lopez OL, Boller F, Becker JT, Miller M, Reynolds CF. Alzheimer's disease and depression: neuropsychological impairment and progression of the illness. *Am J Psychiatry.* 1990;147:855-860.

9. Ingvar DH, Franzen G. Abnormalities of cerebral blood flow distribution in patients with chronic schizophrenia. *Acta Psychiatr Scand.* 1974;50:425-462.

10. Ariel RN, Golden CJ, Berg RA, et al. Regional cerebral blood flow in schizophrenics. *Arch Gen Psychiatry.* 1983;40:258-263.

11. Chabrol H, Guell A, Bes A, Moron P. Cerebral blood flow in schizophrenic adolescents. *Am J Psychiatry.* 1986;143:130.

12. Weingerg DR, Berman KF, Zec RF. Physiologic dysfunction of dorsolateral prefrontal cortex in schizophrenia. *Arch Gen Psychiatry.* 1986;43:114-124.

13. Buchsbaum MS, Ingvar DH, Kessler R, et al. Cerebral glucography with positron tomography. *Arch Gen Psychiatry.* 1982;39:251-259.

14. Buchsbaum MS, DeLisi LE, Holcomb HH, et al. Anteroposterior gradients in cerebral glucose use in schizophrenia and affective disorders. *Arch Gen Psychiatry.* 1984;41:1159-1166.

15. Wolkin A, Jaeger J, Brodie JD, et al. Persistence of cerebral metabolic abnormalities in chronic schizophrenia as determined by positron emission tomography. *Am J Psychiatry.* 1985;142:564-571.

16. Kling AS, Metter EJ, Riege WH, Kuhl DE. Comparison of PET measurement of local brain glucose metabolism and CAT measurement of brain atrophy in chronic schizophrenia and depression. *Am J Psychiatry.* 1986;143:175-180.

17. Kovelman JA, Schiebel AB. A neurohistological correlate of schizophrenia. *Biol Psychiatry.* 1984;19:1601-1621.

18. Benes FM, Davidson J, Bird ED. Quantitative cytoarchitectural studies of the cerebral cortex of schizophrenics. *Arch Gen Psychiatry.* 1986;43:31-135.

19. Altshuler LL, Conrad A, Kovelman JA, Schiebel AB. Hippocampal pyramidal cell orientation of schizophrenia. *Arch Gen Psychiatry.* 1987;44:1094-1098.

20. Benes FM, Majocha R, Bird ED, Marotta CA. Increased cervical axon numbers in cingulate cortex of schizophrenics. *Arch Gen Psychiatry.* 1987;44:1017-1021.

21. Christison GW, Casanova MF, Weinberg DR, Rawlings R, Kleinman JE. A quantitative investigation of hippocampal pyramidal cell size, shape, and variability of orientation in schizophrenia. *Arch Gen Psychiatry.* 1989;46:1027-1032.

22. Jeste DV, Lohr JB. Hippocampal pathologic findings in schizophrenia: a morphometric study. *Arch Gen Psychiatry.* 1989;46:1019-1024.

23. Zubenko GS, Moossy J, Kopp U. Neurochemical correlates of major depression in primary dementia. *Arch Neurol.* 1990;47:209-214.

24. McKhann G, Brachman D, Folstein M, Katzman R, Price D, Stadlan E. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of the Department of Health and Human Task Force of Alzheimer's disease. *Neurology.* 1984;34:939-944.

25. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders-Revised.* 3rd ed. Washington, DC: American Psychiatric Association; 1987.

26. Zubenko GS, Cohen BM, Reynolds CF, Boller F, Malinakova I, Keefe N. Platelet membrane fluidity in Alzheimer's disease and major depression. *Am J Psychiatry.* 1987;144:860-868.

27. Huff FJ, Becker JT, Belle SH, Nebes RD, Holland AL, Boller F. Cognitive deficits and clinical diagnosis of Alzheimer's disease. *Neurology.* 1987;37:1119-1124.

28. Huff FJ, Boller F, Lucchelli F, Querriera R, Beyer J, Belle S. The neurologic examination in patients with probable Alzheimer's disease. *Arch Neurol.* 1987;44:929-932.

29. Khachaturian ZS. Diagnosis of Alzheimer's disease. *Arch Neurol.* 1985;42:1097-1105.

30. Mezzich JE, Dow JT, Rich CL, Costello AJ, Himmelhoch JM. Developing an efficient clinical information system for a comprehensive psychiatric institute, II: initial evaluation form. *Behav Res Meth Instrument.* 1981;13:464-478.

31. Mezzich JE, Fabrega H, Coffman GA, Glavin YFG. Comprehensively diagnosing geriatric patients. *Comp Psychiatry.* 1987;28:68-76.

32. Mezzich JE, Fabrega H, Coffman GA, Haley R. DSM-III disorders in a large sample of psychiatric patients: frequency and specificity of diagnoses. *Am J Psychiatry.* 1989;146:212-219.

33. Moossy J, Zubenko GS, Martinez AJ, Rao GR. Bilateral symmetry of morphologic lesions in Alzheimer's disease. *Arch Neurol.* 1988;45:251-254.

34. Zubenko GS, Moossy J, Hanin I, Martinez AJ, Rao GR, Kopp U. Bilateral symmetry of cholinergic deficits in Alzheimer's disease. *Arch Neurol.* 1988;45:255-259.

35. Saller CF, Salama AI. Rapid automated analysis of biogenic amines and their metabolites using reversed-phase high performance liquid chromatography with electrochemical detections. *J Chromatogr.* 1984;309:287-298.

36. Zubenko GS, Moossy J, Kopp U. Neurochemical correlates of major depression in primary dementia. *Arch Neurol.* 1990;47:209-214.

37. Palmer AM, Francis PT, Bowen DM, et al. Catecholaminergic neurons assessed antemortem in Alzheimer's disease. *Brain Res.* 1987;414:365-375.

38. Lowry OH, Rosenbrough NJ, Farr AL, Randall RJ. Protein measurement with the Folin phenol reagent. *J Biol Chem.* 1951;193:265-275.

39. Fonnum F. Radiochemical micro assays for the determination of choline acetyltransferase and acetylcholinesterase activity. *Biochem J.* 1969;115:465-472.

40. Zubenko GS, Moossy J, Claassen D, Martinez AJ, Rao GR. Brain regional analysis of NADH-cytochrome C reductase activity in Alzheimer's disease. *J Neuropathol Exp Neurol.* 1990;49:206-214.

41. Zubenko GS. Biological correlates of clinical heterogeneity in primary dementia. *Neuropsychopharmacology.* In press.

42. Rovner BW, Broadhead J, Spencer M, Carson K, Folstein MF. Depression and Alzheimer's disease. *Am J Psychiatry.* 1989;146:350-354.

43. Hoch CC, Reynolds CF, Houck PR, et al. REM latency and apnea-hypopnea index predict two-year mortality in mixed depressed-demented patients. *J Neuropsychiatr Clin Neurol.* In press.

Regional Cerebral Blood Flow After Human Cardiac Arrest

A Hexamethylpropyleneamine Oxime Single Photon Emission Computed Tomographic Study

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• We studied 30 patients 24 hours after out-of-hospital cardiac arrest and 13 age-matched normal controls with the use of technetium Tc 99m–hexamethylpropyleneamine oxime single photon emission computed tomography. All patients were followed up for 12 months or until death. Frontal hypoperfusion (anteroposterior perfusion ratio, <0.90) was observed in 23 patients (77%). In eight patients who remained comatose and died, the total size of perfusion defects was larger (38% ± 20%) than in the 21 patients who recovered consciousness (24% ± 14%), but the anteroposterior ratio was similar in both of these patient groups (0.83 ± 0.09) and significantly lower than in the controls (0.96 ± 0.03). During follow-up, both the anteroposterior perfusion ratio and the relative defect size improved, but frontal hypoperfusion was still observed in seven of 13 patients. After cardiac arrest, regional cerebral blood flow is characterized by frontal hypoperfusion that tends to improve over time but that persists in most patients.

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The recovery of cerebral blood flow (CBF) is essential for the survival of cardiac arrest victims. In experimental animal models, global cerebral ischemia can result in generalized or patchy hypoperfusion.[1,2] Multifocally reduced CBF following cardiac arrest has recently been reported by stable xenon computed tomographic and microsphere methods in dogs without correlation to neurological outcome.[3,4] The regional distribution of CBF (rCBF) after human cardiac arrest is still unknown. Neither is it known whether changes in postischemic CBF have any correlation with recovery of consciousness or outcome. Delayed restoration of spontaneous circulation has been shown to be detrimental to the recovery of CBF.[5,6]

Single photon emission computed tomography (SPECT) and lipophilic tracers, especially technetium Tc 99m–hexamethylpropyleneamine oxime (HMPAO), have been used clinically in the evaluation of various conditions such as stroke,[7,8] epilepsy,[9] dementia,[10] subarachnoid hemorrhage,[11] encephalitis,[12] and brain death.[13,14] HMPAO readily crosses the blood-brain barrier and has a high first-pass cerebral extraction with satisfactory retention for imaging purposes.[15,16] Some studies suggest that HMPAO SPECT may be useful in predicting the outcome of stroke,[8,17] but contradictory results have also been published.[18,19]

We studied the rCBF in 30 patients who had been resuscitated from out-of-hospital ventricular fibrillation 24 hours after cardiac arrest, and we repeated the examination several weeks later using ^{99m}Tc-HMPAO and SPECT. The aims of this study were as follows: (1) to find out whether a characteristic pattern of CBF exists after human cardiac arrest; (2) to see how the regional flow changes during follow-up; (3) to evaluate the prognostic value of SPECT in the acute postarrest stage; and (4) to study the effect of a calcium entry–blocking drug, nimodipine, on the rCBF after cardiac arrest.

PATIENTS AND METHODS

We studied 30 patients (mean [± SD] age, 65 ± 12 years) 24 ± 2 hours after resuscitation from out-of-hospital ventricular fibrillation, and 13 age-matched normal controls without diagnosed cerebral disorders (mean [± SD] age, 64 ± 6.5 years). All patients included in the study had been recruited in a placebo-controlled double-blind trial of nimodipine in the treatment of out-of-hospital ventricular fibrillation, in which a total of 155 patients were enrolled.[20] Seventeen patients received a continuous infusion of nimodipine in a dosage of 0.5 μg/kg per minute for 24 hours and 13 received placebo. Informed consent was obtained from a family member of the patient. During the first 24 hours after cardiac arrest, all patients were treated according to a standardized, brain-oriented intensive care protocol. All patients received controlled ventilation during SPECT with a mean arterial Pco$_2$ of 31 ± 5.6 mm Hg. The duration of arrest without cardiopulmonary resuscitation was 5.6 ± 2.1 minutes, and spontaneous circulation was restored in 18.3 ± 5.2 minutes after arrest time. The level of consciousness of each patient at the time of SPECT was assessed using the Glasgow Coma Scale.[21]

Single photon emission computed tomographic imaging was performed with a rotating large field-of-view gamma camera (General Electric 400T, General Electric, Hoersholm, Denmark) equipped with a low-energy all-purpose parallel hole collimator. Three hundred seventy to seven hundred forty megabequerels of HMPAO labeled with technetium Tc 99m and 30 seconds per frame was used. Filtered back projection algorithm using a modified Shepp-Logan filter

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Table 1.—Clinical and Single Proton Emission Computed Tomographic (SPECT) Data 24 Hours After Cardiac Arrest in 21 Patients Recovering Consciousness and in Nine Patients Remaining Comatose Until Death*

Case/Sex/ Age, y	Nimodipine/ P	Arrest, min	Pco$_2$, mm Hg	GCS	Coma, h	GOS	MMSE	Survival, d	A/P Ratio	Defect Count	Defect, %	CT	MRI	Perfusion Defect
Consciousness Recovered														
1/M/73	P	1	36	14	9	5	28	>365	0.84	3	31.3	Normal	Normal	Frontal
2/M/43	Nimodipine	2	20	11	15	5	30	>365	0.75	2	38.3	NA	NA	Frontal
3/M/49	P	3	24	15	9	5	28	>365	0.86	3	30.5	Normal	Normal	Frontal
4/M/57	Nimodipine	3	20	8	34	5	29	>365	0.89	3	19.2	NA	Normal	R and L fronto-parietal
5/M/61	Nimodipine	4	18	10	31	1	NA	4	0.80	1	34.5	NA	NA	Frontal
6/F/66	P	4	19	10	23	4	26	>365	0.87	4	20.9	Abnormal	NA	Frontal
7/F/76	Nimodipine	4	23	14	12	5	28	>365	0.83	0	0.0	NA	NA	None
8/F/79	P	5	22	9	6	5	27	>365	0.83	3	8.6	NA	Abnormal	L frontal and temporal
9/M/57	P	5	19	7	29	1	NA	66	0.97	2	10.0	NA	NA	R frontal, L parietal
10/F/48	Nimodipine	5	14	8	312	3	0	294	0.74	1	23.7	Abnormal	Abnormal	Frontal
11/M/61	Nimodipine	5	26	10	17	5	27	>365	0.79	1	37.8	Normal	Abnormal	Frontal
12/M/76	Nimodipine	5	16	15	2	5	28	>365	0.74	4	10.9	Normal	NA	Frontal
13/F/67	Nimodipine	5	13	10	22	5	25	>365	0.92	2	11.4	Normal	NA	L temporal, R parietal
14/M/58	P	5	24	11	27	5	29	>365	0.81	2	24.7	Abnormal	NA	Frontal, R temporal hyperperfusion
15/M/83	Nimodipine	5	18	11	15	4	20	>365	0.77	2	46.0	Abnormal	Abnormal	Frontal
16/M/61	Nimodipine	6	25	15	7	5	30	>365	0.55	1	38.8	Abnormal	Abnormal	Frontal
17/M/56	P	7	20	15	4	5	30	>365	0.83	1	42.3	NA	Abnormal	Frontal
18/M/63	Nimodipine	7	20	14	12	5	30	>365	0.91	1	26.8	NA	NA	Frontal
19/M/56	P	7	19	6	29	5	30	>365	0.88	0	0.0	Normal	Normal	None
20/F/61	Nimodipine	8	17	6	48	1	NA	18	0.82	1	14.9	NA	NA	Frontal
21/F/71	Nimodipine	10	20	9	384	3	7	>365	0.91	3	23.3	NA	NA	R and L fronto-temporal
Irreversible Coma														
22/M/70	P	4	18	6	...	1	NA	39	0.99	3	20.3	Abnormal	NA	R and L parieto-occipital
23/M/79	Nimodipine	5	16	8	...	1	NA	5	0.77	2	54.6	NA	NA	Frontal
24/M/72	P	6	17	6	...	1	NA	2	0.89	2	22.0	NA	NA	L frontal, R occipital
25/M/65	P	6	25	9	...	1	NA	56	0.68	1	57.7	NA	NA	Frontal
26/F/85	Nimodipine	7	26	3	...	1	NA	3	...	1	100.0	NA	NA	Missing CBF
27/M/75	Nimodipine	7	15	6	...	1	NA	3	0.75	1	63.9	NA	NA	Frontal
28/M/75	Nimodipine	8	23	7	...	1	NA	16	0.94	2	28.2	NA	NA	Frontal
29/M/79	P	8	23	5	...	1	NA	11	0.86	3	10.8	NA	NA	R and L parietal
30/M/41	P	11	18	6	...	1	NA	16	0.75	1	44.4	NA	NA	Frontal

*A/P ratio denotes the activity ratio of frontal and occipital brain regions; defect %, the total relative size of supratentorial perfusion defects; P, placebo, Pco$_2$, arterial blood carbon dioxide partial pressure during SPECT; GCS, Glasgow Coma Score during SPECT; GOS, Glasgow Outcome Score at 1 year; MMSE, Mini-Mental State Examination at 1 year; R, right; L, left; NA, not available; and CBF, cerebral blood flow.

was used for producing a set of eight 15-mm-thick transversal tomographic slices from the orbitomeatal line upwards. The data acquisition was started 2 minutes after the injection of the tracer into an antecubital vein. A second scan was performed on 13 patients an average of 145 days later (range, 9 to 437 days).

As absolute rCBF cannot be measured by this technique, a comparison of count rates between hemispheres and the relative rCBF values using cerebellum as an intraindividual reference are commonly used semiquantitative indexes of regional abnormalities of blood flow. However, bilateral or diffuse perfusion defects expected to occur after global cerebral ischemia may remain unnoticed by such methods. Thus, we used two other indexes of rCBF: (1) the total size of perfusion defects (ie, defect percentage), expressed as percentage of the total supratentorial brain volume as determined visually and measured by planimetry; and (2) the anteroposterior perfusion (A/P) ratio, expressed as the ratio of the count-rates in frontal and occipital thirds of four superimposed supratentorial slices. An A/P ratio below 2 SDs of the mean of age-matched controls (ie, <0.90) was considered to indicate frontal hypoperfusion.

Computed tomography (12 studies) or low-field magnetic resonance imaging (10 studies) was performed more than 2 weeks after arrest on 15 patients. Seven patients underwent both studies.

All patients were followed up for 12 months or until death. At 12 months, a neurological examination, Mini-Mental State Examination,[22] neuropsychological examinations, and assessment of activities of daily living functions and quality of life were performed for survivors. These findings will be reported separately. The 1-year outcome of all survivors was graded using the Glasgow Outcome Scale.[23]

All values are expressed as means ± SDs and/or 95% confidence intervals (CI). For statistical comparison of group means, unpaired or paired *t* tests with two-tailed *P* values and 95% CI of the mean were used for continuous variables.

RESULTS

In the first study, SPECT was abnormal in 28 patients and normal in only two patients (Table 1). One patient (case 26) with complete lack of intracranial circulation and brain death was excluded from further statistical analysis. The mean relative size of the perfusion defect was 29.9% ± 20.9% (95% CI, 22.0 to 37.7). The mean A/P ratio was 0.83 ± 0.09 (95% CI, 0.79 to 0.86) and was significantly lower than in age-matched controls (0.96 ± 0.03; 95% CI, 0.94 to 0.98, *P*<.001) (Table 2, Fig 1). Frontal hypoperfusion (A/P ratio <0.90) was observed in 23 patients

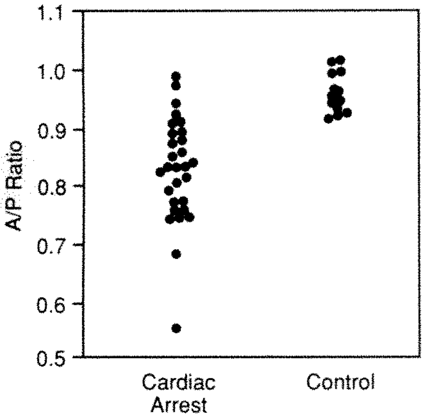

Fig 1.—Anteroposterior perfusion ratio (A/P ratio) in 29 patients who suffered cardiac arrest 24 hours after arrest and in 13 age-matched controls.

(77%) (Fig 2), a single perfusion defect was observed in 10 patients (33%), and two to five defects were observed in nine patients (30%) (Table 1). The localization of separate perfusion defects varied widely. Crossed cerebellar diaschisis was observed in nine patients.

Nine patients remained comatose and died, whereas 21 patients recovered consciousness. The mean duration of coma was 50 hours (range, 2 hours to 56 days). Seventeen patients survived for at least 1 year. In eight patients dying while in a comatose state, the perfusion defect was larger (38%±20%) than in the 21 patients who recovered consciousness (24%±14%, $P=.035$) (Table 2). However, the perfusion defect size did not correlate with the Glasgow Outcome Score at 1 year after cardiac arrest.

In the second study, both the A/P perfusion ratio and the relative defect size had improved, but frontal hypoperfusion was still present in seven of 13 patients (Table 3). The A/P ratio was below 0.80 in only one patient (case 10) in the second SPECT. She had a severe anoxic encephalopathy leading to death 294 days after the arrest. Another patient with good outcome (case 16) had an A/P perfusion ratio of 0.55 at 24 hours after arrest and 0.83 after 3 months. Five of the seven patients with frontal hypoperfusion still present in the second study reached the best Glasgow Outcome Score at 1 year, one patient (case 6, A/P perfusion ratio of 0.80) had a moderate disability, and one patient (case 10, A/P perfusion ratio of 0.78) had a severe disability. Neither the A/P perfusion ratio nor the defect size correlated with patient age, the arrest time, the duration of resuscitation, or the arterial P_{CO_2} at the time of imaging.

Table 2.—Anteroposterior Perfusion Ratio (A/P Ratio) and Relative Size of Perfusion Defect Expressed as a Percentage of All the Supratentorial Slices in HMPAO SPECT (Defect %) in Patients Recovering Consciousness After Cardiac Arrest and in Those Remaining Comatose Until Death*

	Consciousness Recovered (N = 21)		**Irreversible Coma (N = 8)**		**Controls (N = 13)**	
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**
A/P ratio	0.83 ± 0.09	0.79-0.86	0.83 ± 0.11	0.75-0.90	0.96 ± 0.03†‡	0.94-0.98
Defect, %	24 ± 14	18-30	38 ± 20§	24-52	...	...
Age, y	63 ± 11	58-67	69 ± 13	61-78	64 ± 7	60-67

*The results in 13 age-matched controls are also included. Mean ± SD and 95% confidence intervals (95% CI) are given. HMPAO SPECT indicates technetium Tc 99m-hexamethylpropyleneamine oxime single photon emission computed tomography.

†$P=.00003$ (group 1 and controls).

‡$P=.001$ (group 2 and controls).

§$P=.035$ (groups 1 and 2).

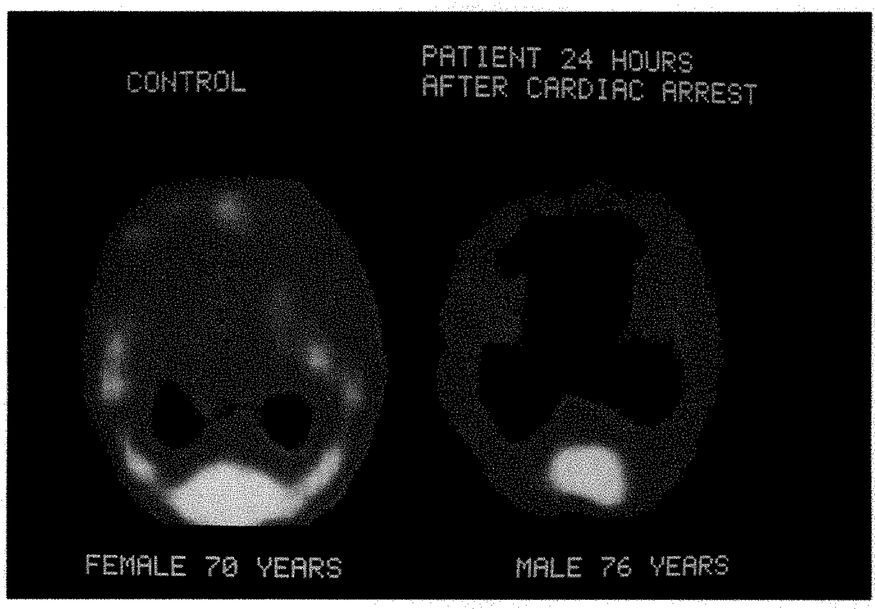

Fig 2.—Left, Control patient (aged 70 years) with normal distribution of regional cerebral blood flow. Anteroposterior (A/P) ratio=0.91. Right, Patient (case 27, aged 76 years) with severe frontal hypoperfusion who underwent hexamethylpropyleneamine oxime single photon emission computed tomography 24 hours after cardiac arrest. The A/P ratio=0.75 and the total size of perfusion defects=63.9% of the supratentorial brain volume. The patient died 2 days later without having recovered consciousness.

Table 3.—Comparison of Short-term and Late Single Photon Emission Computed Tomographic (SPECT) Results*

	Study 1 (N = 13)		**Study 2 (N = 13)**		**Controls (N = 13)**	
	Mean ± SD	**95% CI**	**Mean ± SD**	**95% CI**	**Mean ± SD**	**95% CI**
A/P ratio	0.82 ± 0.10	0.76-0.87	0.88 ± 0.07†	0.84-0.92	0.96 ± 0.03‡§	0.94-0.98
Defect, %	21 ± 13	14-28	10 ± 14†	3-18	...	...
Age, y	61 ± 11	56-67	61 ± 11	56-67	64 ± 7	60-67

*Anteroposterior perfusion ratio (A/P ratio) and relative size of perfusion defect as expressed as a percentage of all the supratentorial slices in technetium Tc 99m-hexamethylpropyleneamine oxime (HMPAO) SPECT (defect %) in patients imaged twice by HMPAO SPECT. The results in 13 age-matched controls are also included. Mean ± SD and 95% confidence intervals (95% CI) are given.

†$P=.03$ (study 1 and 2).

‡$P=.006$ (study 2 and controls).

§$P=.0001$ (study 1 and controls).

Table 4.—Mean Perfusion Defect Size (Defect %) and Anteroposterior Perfusion Ratio (A/P Ratio) After Cardiac Arrest in Patients Receiving Nimodipine or Placebo*

	Nimodipine (N = 16)	Placebo (N = 13)
Defect, %	29.5 (21.0-38.0)	24.9 (15.4-34.4)
A/P ratio	0.81 (0.76-0.85)	0.85 (0.80-0.90)

*The numbers in parentheses are 95% confidence intervals.

Of the 17 patients surviving for at least 1 year, 14 had frontal hypoperfusion and three did not have this finding at 24 hours after arrest. Frontal hypoperfusion was as common and as severe in surviving patients as in those remaining comatose until death (Table 2). Thus, frontal hypoperfusion did not predict the outcome. The mean Mini-Mental State Examination score for all 1-year survivors was 26.6±5.6 (95% CI, 23.7 to 29.5), which is in the normal range. The performance in the Mini-Mental State Examination at 1 year after cardiac arrest had no significant correlation to the results of SPECT (Table 1).

Computed tomography revealed vascular lesions in six patients, correlating exactly with the perfusion defect observed in the early SPECT in one patient only. Furthermore, the perfusion defects observed in SPECT corresponded to the vascular lesions found in later magnetic resonance imaging studies in only one of four patients. Both the defect percentage and the A/P ratio were slightly more abnormal in patients receiving nimodipine than in patients receiving placebo, although this difference was not significant (Table 4).

COMMENT

In this study, we detected in most patients 24 hours after cardiac arrest a typical rCBF pattern of frontal hypoperfusion that ameliorated over time but persisted in many cases. Also, the relative size of the total perfusion defect improved in recovering patients. Although permanent unconsciousness was usually associated with a large volume of poorly perfused brain, only the largest perfusion defects seemed to predict irreversible coma. All four patients with a total perfusion defect size of more than 50% of the supratentorial brain remained comatose and died. In the total group of patients who had suffered cardiac arrest, even large perfusion defects (up to 42%) did not exclude the possibility of good recovery and thus the number or size of separate perfusion defects was not a reliable predictor of outcome. The occurrence or severity of frontal hypoperfusion did not predict either the recovery of consciousness or the outcome.

The significance of postischemic hypoperfusion is still equivocal in humans. Based on animal experiments, it is not known whether postischemic hypoperfusion is the cause or the consequence of delayed neuronal injury. Frontal hypoperfusion disappearing in parallel with recovery has previously been reported in patients with posttraumatic coma using the xenon 133 inhalation technique.[24,25] Recently, DeVolder et al[26] demonstrated a generalized decrease in glucose metabolism approximately 1 to 6 months after cardiac arrest in 12 patients by positron emission tomography and 2-[^{18}F] fluoro-2-deoxy-D-glucose. They found frontal hypometabolism in five of 12 patients, whereas a regional decrease in fluorodeoxyglucose uptake was more common in the parieto-occipital cortex (nine of 12 patients). In seven patients who underwent imaging scans while in a vegetative state, the mean cerebral glucose metabolism was about 50% of that observed in control patients.[26] Beckstead and coworkers,[27] using inhaled xenon and extracranial detectors, were the first to detect a decreased cortical CBF during the first 2 hours after arrest but a normal CBF 24 hours later in 25 patients. According to Forsman et al,[28] nimodipine increases postischemic CBF in man without an effect on neurological outcome. They demonstrated that the mean cortical CBF was only 13±1 mL/100 g per minute 3 to 4 hours after arrest in their series of 51 patients. The mean cortical CBF did not correlate with the recovery of consciousness, but nimodipine roughly doubled the mean CBF. The effect of nimodipine on the evolution of human cerebral infarction has also been studied by positron emission tomography.[29] Patients receiving intravenous nimodipine for 1 week after a hemispheric ischemic stroke had significantly higher rCBF values in the densely ischemic areas as compared with those receiving placebo. Although the aim of many therapeutic approaches has been to augment postischemic CBF, an increase in CBF has also been reported to be associated with irreversible brain damage and death after cardiac arrest.[30]

One of the goals of the present study was to find out the possible effect of nimodipine on the postischemic rCBF. We found no evidence of a beneficial effect of nimodipine on frontal postischemic hypoperfusion or rCBF as measured by the defect percentage after cardiac arrest. On the other hand, CBF changes occurring during the early postischemic phase as well as all quantitative changes in the mean CBF would have remained unnoticed in the present study.

Most regional perfusion defects imaged by SPECT in the early phase after cardiac arrest were not observed in later neuroradiological examinations, ie, did not lead to completed infarction. In general, the perfusion defect in SPECT is larger than the corresponding infarction visualized later with computed tomography or magnetic resonance imaging, which has been suggested to be associated with the capacity of SPECT to visualize the peri-infarct zone with reduced blood flow.[31]

In recovering patients, both the A/P perfusion ratio and the defect percentage improved significantly, but frontal hypoperfusion still remained in seven of 13 patients. Five patients had a good outcome despite the persisting frontal hypoperfusion and only those two with the lowest A/P perfusion ratios in the second study were disabled. The A/P ratio was the same in patients recovering consciousness and in those who did not. Furthermore, two of the eight patients remaining comatose until death after 16 or 39 days had a completely normal A/P ratio (0.94 and 0.99, respectively). Even recovering patients had a significantly worse A/P perfusion ratio in both short-term and late studies as compared with age-matched controls. According to the results of this study, a severe frontal hypoperfusion seems to be a characteristic finding after human cardiac arrest, although it is not always present. Additionally, frontal hypoperfusion did not seem to reflect coma as might be the case after head trauma.[24,25]

After cardiac arrest, the rCBF improves after the acute stage in recovering patients but may remain abnormal. Technetium Tc 99m–HMPAO SPECT may have some value as an additional prognostic indicator early after cardiac arrest. It is capable of visualizing poor circulation in extensive regions of the brain thereby suggesting bad outcome as well as the complete lack of intracranial circulation in brain death. Quantitative measurement of rCBF and metabolism is likely to provide more useful information of the potential of the brain to recover from global ischemia and to direct future attempts in cerebral resuscitation.

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References

1. Ames A, Wright RL, Kowada M, Thurston JM, Majno G. Cerebral ischemia, II: the no-reflow phenomenon. *Am J Pathol.* 1968;52:437-453.

2. White BC, Winegar CP, Henderson O, et al. Prolonged hypoperfusion in the cerebral cortex following cardiac arrest and resuscitation in dogs. *Ann Emerg Med.* 1983;12:414-417.

3. Wolfson SK, Safar P, Reich H, Clark J, Gur D. Multifocal, dynamic cerebral hypoperfusion after prolonged cardiac arrest in dogs, measured by the stable xenon-CT technique. *Crit Care Med.* 1988;16:390. Abstract.

4. LaManna JC, Crumrine C, Jackson DL. No correlation between cerebral blood flow and neurologic recovery after reversible total cerebral ischemia in the dog. *Exp Neurol.* 1988;101:234-247.

5. Lee SK, Vaagenes P, Safar P, Stezoski SW, Scanlon M. Effect of cardiac arrest time on the cortical cerebral blood flow generated by subsequent standard external CRP in rabbits. *Ann Emerg Med.* 1984;13:385. Abstract.

6. Scharff JA, Pantley G, Noel E. Effect of time on regional organ perfusion during two methods of cardiopulmonary resuscitation. *Ann Emerg Med.* 1984;13:649-656.

7. Ell PJ, Hocknell JML, Jarritt PH, et al. A Tc-99m-labelled radiotracer for the investigation of cerebral vascular disease. *Nucl Med Commun.* 1985;6:437-441.

8. Launes J, Nikkinen P, Lindroth L, Brownell A-L, Liewendahl K, Iivanainen M. Brain perfusion defect size in SPECT predicts outcome in cerebral infarction. *Nucl Med Commun.* 1989;10:891-900.

9. Grünwald F, Durwen H, Bülan P, et al. HMPAO-SPECT in cerebral seizures. *Nucl Med.* 1988;27:248-251.

10. Smith FW, Gemmel HG, Sharp PF. The use of ^{99}Tc^{m}-HM-PAO for the diagnosis of dementia. *Nucl Med Commun.* 1987;8:525-533.

11. Davis S, Andrews J, Lichtenstein M, et al. A single-photon emission computed tomography study of hypoperfusion after subarachnoid hemorrhage. *Stroke.* 1990;21:252-259.

12. Launes J, Nikkinen P, Lindroth L, Brownell A-L, Liewendahl K, Iivanainen M. Diagnosis of acute herpes simplex encephalitis by brain perfusion single photon emission computed tomography. *Lancet.* 1988;2:1188-1191.

13. Roine RO, Launes J, Lindroth L, Nikkinen P. ^{99m}Tc-Hexamethylpropyleneamine oxime scans to confirm brain death. *Lancet.* 1986;2:1223-1224.

14. Laurin NR, Driedger AA, Hurwitz GA, et al. Cerebral perfusion imaging with technetium-99m HM-PAO in brain death and severe central nervous system injury. *J Nucl Med.* 1989;30:1627-1635.

15. Andersen AR, Friberg HH, Knudsen KBM, et al. Extraction of [99mTc]-d,l-HM-PAO across the blood-brain barrier. *J Cereb Blood Flow Metab.* 1988;8(suppl 1):44-51.

16. Lassen NA, Andersen AR, Friberg L, Paulson OB. The retention of [99mTc]-d,l-HM-PAO in the human brain after intracarotid bolus injection: a kinetic analysis. *J Cereb Blood Flow Metab.* 1988;8(suppl 1):13-22.

17. Bushnell DL, Gupta S, Mlcoch AG, Barnes WE. Prediction of language and neurologic recovery after cerebral infarction with SPECT imaging using N-isopropyl-*p*-(I 123) iodoamphetamine. *Arch Neurol.* 1989;46:665-669.

18. Lee RG, Hill TC, Holman BL, Royal HD, O'Leary DH, Clouse ME. Predictive value of perfusion defect site using N-isopropyl-(I-123)-p-iodoamphetamine emission tomography in acute stroke. *J Neurosurg.* 1984;61:449-452.

19. Hayman LA, Taber KH, Jhingran SG, Killian JM, Carroll RG. Cerebral infarction: diagnosis and assessment of prognosis by using ^{123}IMP-SPECT and CT. *AJNR.* 1989;10:557-562.

20. Roine RO, Kaste M, Nikki P, Kinnunen A. Randomized double-blind trial of nimodipine in out-of-hospital resuscitation. *Stroke.* 1990;21:178. Abstract.

21. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;2:81-83.

22. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

23. Jennett B, Bond M. Assessment of outcome after severe brain damage: a practical scale. *Lancet.* 1975;1:480-484.

24. Deutsch G, Eisenberg HM. Frontal flow changes in recovery from coma. *J Cereb Blood Flow Metab.* 1987;7:29-34.

25. Obrist WD, Langfitt TW, Jaggi JL, Cruz J, Gennarelli TA. Cerebral blood flow and metabolism in comatose patients with acute head injury. *J Neurosurg.* 1984;61:241-253.

26. DeVolder AG, Goffinet AM, Bol A, Michel C, de Barsy T, Laterre C. Brain glucose metabolism in postanoxic syndrome: positron emission tomographic study. *Arch Neurol.* 1990;47:197-204.

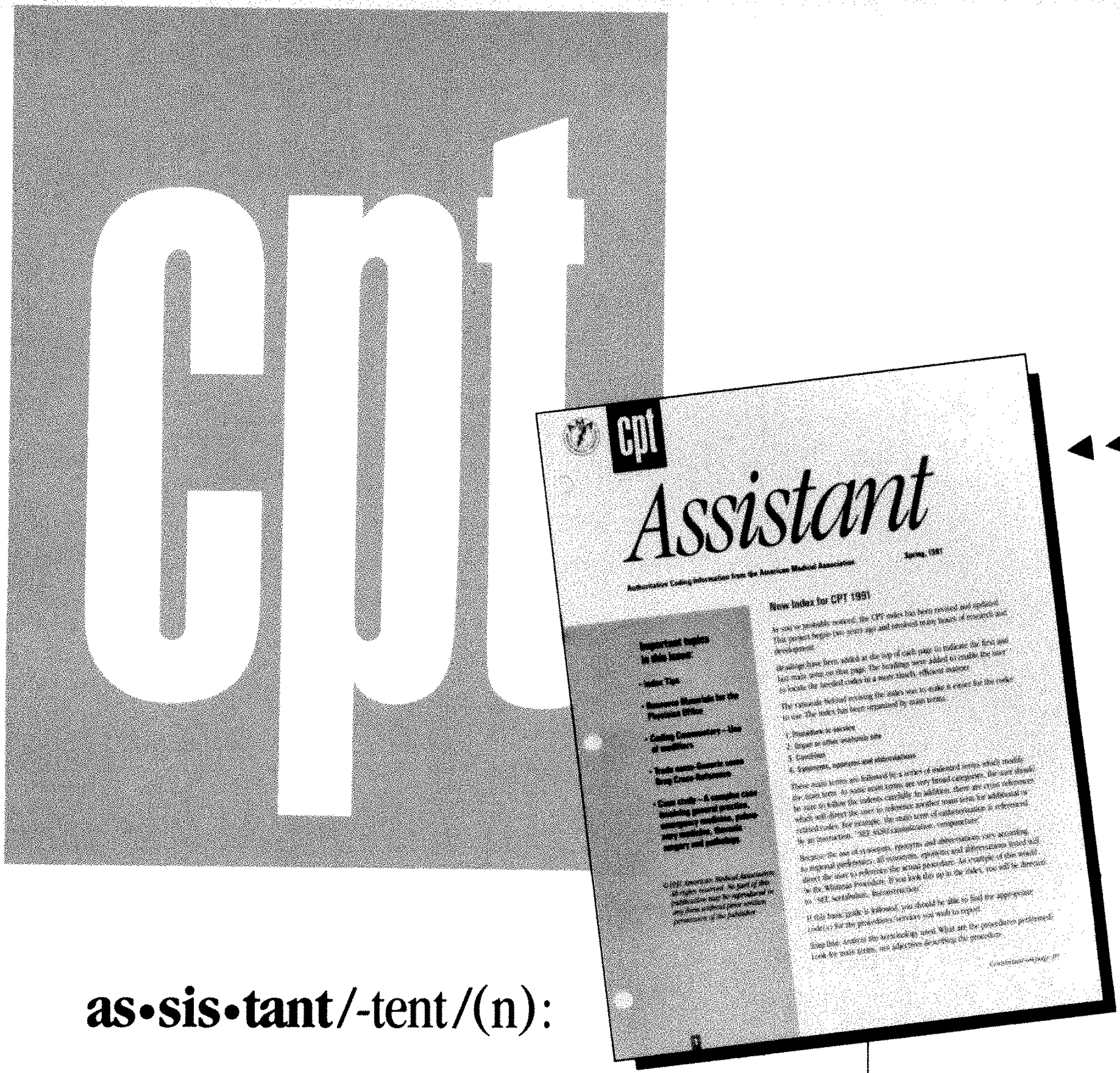
27. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. *Stroke.* 1978;9:569-573.

28. Forsman M, Aarseth HP, Nordby HK, Skulgerg A, Steen PA. Effects of nimodipine on cerebral blood flow and cerebrospinal fluid pressure after cardiac arrest: correlation with neurologic outcome. *Anesth Analg.* 1989;68:436-443.

29. Hakim AM, Evans AC, Berger L, et al. The effect of nimodipine on the evolution of human cerebral infarction studied by PET. *J Cereb Blood Flow Metab.* 1989;9:523-534.

30. Cohan SL, Mun SK, Petite J, Correia J, Taveira Da Silva A, Waldhorn RE. Cerebral blood flow in humans following resuscitation from cardiac arrest. *Stroke.* 1989;20:761-765.

31. Raynaud C, Rancurel G, Samson Y, et al. Pathophysiologic study of chronic infarcts with I-123 isopropyl iodo-amphetamine (IMP): the importance of periinfarct area. *Stroke.* 1987;18:21-29.



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Sclerosing Vasculopathy of the Central Nervous System in Nonelderly Demented Patients

Melinda L. Estes, MD; Marc I. Chimowitz, MD; Issam A. Awad, MD;
James T. McMahon, PhD; Anthony J. Furlan, MD; Norman B. Ratliff, MD

• Three nonelderly patients without hypertension whose clinical and radiologic features otherwise resembled Binswanger's subcortical arteriosclerotic encephalopathy underwent biopsy of the hyperintense periventricular lesions seen on magnetic resonance imaging. The pathologic findings of the periventricular lesions consisted of gliosis with mild rarefaction and edema of the white matter. All patients had a sclerosing vasculopathy of unknown cause, which involved numerous small vessels within the periventricular lesions. The vessels stained negatively for amyloid, amyloid precursors, desmin, vimentin, keratin, immunoglobulin, and complement. On electron microscopy, small arteries, arterioles, venules, and capillaries were characterized by swollen astrocytic foot processes surrounding the vessels; dense, perivascular collagen packing; crystalline arrays of filaments within basement membrane; giant lipid-laden lysosomes within perivascular cells; and narrowing of the vascular lumina. Similar changes were not seen in a control group of 19 patients. The pathologic features of the vessels in these cases are distinct from the vasculopathy associated with Binswanger's subcortical arteriosclerotic encephalopathy. We suggest that a spectrum of vasculopathies may be associated with dementia and periventricular hyperintense lesions on magnetic resonance imaging.

(*Arch Neurol.* 1991;48:631-636)

Although numerous articles[1-9] have described the clinical, radiological, and pathological features of Binswanger's subcortical arteriosclerotic encephalopathy (BSAE) and although the white matter lesions in patients with BSAE are well documented, the vasculopathy associated with this syndrome is not well characterized. Most articles describe the vascular lesions as arteriosclerosis or lipohyalinosis, without providing ultrastructural details of the vessels. We had the opportunity to study three nonelderly patients without hypertension, in whom clinical and radiological features otherwise resembled BSAE. Examination of brain biopsy specimens obtained from these patients showed distinctive small-vessel lesions that were not seen in specimens from a control group of 19 patients undergoing stereotactic brain biopsy for other reasons. This article describes the clinical, radiological, and pathological features found in the three patients and focuses on the pathological features of the small vessels revealed by means of light and electron microscopic examination.

REPORT OF CASES

CASE 1.—A 48-year-old man was examined in 1988 for progressive dementia. He had a history of throbbing headaches since the age of 10 years, often associated with teichopsia, limb paresthesia, and aphasia. Several medications were prescribed for the headaches, including a combination of caffeine and ergotamine tartrate (Cafergot), methysergide maleate (Sansert), prednisone, and meperidine hydrochloride (Demerol). In 1974, at the age of 34 years, he suddenly developed right hemiparesis, which was persistent and unassociated with his typical migraine headache. In 1981, he was admitted to the psychiatric service for depression and opiate dependence. Neurological examination showed right-sided hyperreflexia and a right-sided Babinski sign. Cranial computed tomographic (CT) scan showed confluent periventricular lucencies. In 1983, he was readmitted to the psychiatric service for depression and opiate dependence. Previously normotensive, his blood pressure on admission was 150/65 mm Hg. His neurological examination results and CT scan were unchanged. A toxicologic profile was positive for amphetamines. By 1985, he had become forgetful and could not handle money. His memory deteriorated progressively, and he developed walking difficulties over the next 3 years, prompting readmission in 1988.

On examination in July 1988, his blood pressure was 125/85 mm Hg. His affect was bland, and responses to questions were slow. He thought it was July 1985. Speech was normal with naming, repetition, reading, and comprehension preserved. He recalled two of four objects at 5 minutes. There was decreased dexterity using the right hand, bilateral arm and leg spasticity with hyperreflexia and ankle clonus, and a right-sided Babinski sign. On walking, his steps were small, slow, and unsteady. Sensation was normal.

The results of cerebrospinal fluid examination, including immunoglobulin studies, were normal except for a slightly elevated

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protein level (62 mg/dL). Magnetic resonance imaging (MRI) showed diffuse confluent areas of increased signal intensity in the periventricular region that contained discrete cystic lesions and mildly enlarged lateral ventricles (Fig 1). Three-vessel cerebral angiographic findings showed no evidence of occlusive disease. Uncertainty regarding the diagnosis prompted a right frontal craniotomy with biopsy of the frontal cortex, centrum semiovale, and periventricular region.

CASE 2.—In 1980, a 48-year-old normotensive woman, with long-standing throbbing headaches, developed dysarthria and began to drag her right leg when walking. In 1982, she was examined for excessive sleepiness and diminished short-term memory. Results of spinal fluid examination were normal, a cranial CT scan showed attenuation of the white matter in the frontal regions, and an electroencephalogram demonstrated frontal, intermittent, rhythmic delta activity. In 1982, a few episodes of confusion, drooling, dysarthria, and urinary incontinence were attributed to seizures prompting treatment with carbamazepine (Tegretol). Over the next 6 years, she developed progressive dementia, urinary incontinence, and difficulty walking.

On examination in 1988, she was inappropriately jovial, inattentive, thought it was 1967, and recalled none of three objects in 5 minutes. Naming, repetition, reading, and writing were relatively well preserved. She drew a clock poorly, but could pantomime simple motor tasks. Her speech was dysarthric, the jaw jerk was prominent, and her right side was moderately weak and spastic. The reflexes were brisk bilaterally, and a right-sided Babinski sign was present. Her gait was wide based, extremely slow, and she exhibited delayed hip flexion and circumduction of the right leg. Sensation was normal, except for diminished vibration appreciation at the ankles.

Spinal fluid examination revealed the following findings: glucose, 3.72 mmol/L; protein, 0.68 g/L; white blood cell count, 1×10^6/L; red blood cell count, 1×10^6/L; IgG, 0.06 (normal, 0.006 to 0.04); albumin, 0.36 (normal, 0.08 to 0.30), IgG-to-albumin ratio, 0.17 (normal 0.07 to 0.19); IgG synthesis, 3.1 mg/d (normal, 0 to 3.1 mg/d); and negative oligoclonal bands. A brain MRI showed diffuse confluent areas of increased signal intensity in the periventricular regions, mildly enlarged ventricles, and moderate cortical atrophy. Results of three-vessel cerebral angiography were normal. Uncertainty regarding the diagnosis prompted stereotactic brain biopsy of the right frontal periventricular region.

CASE 3.—A 40-year-old normotensive man was examined in 1988 for progressive dementia and walking difficulties. Nine years earlier, he was laid off work in an assembly plant. He became depressed, apathetic, and uninterested in social activities. His wife suspected that he was confused at times. At attempt to return to work in 1985 failed because of inability to do his previous job. His memory began to fail, his gait was unsteady, and he fell occasionally. His cognitive and gait difficulties progressed insidiously over the next 3 years, and, ocasionally, he was incontinent of urine.

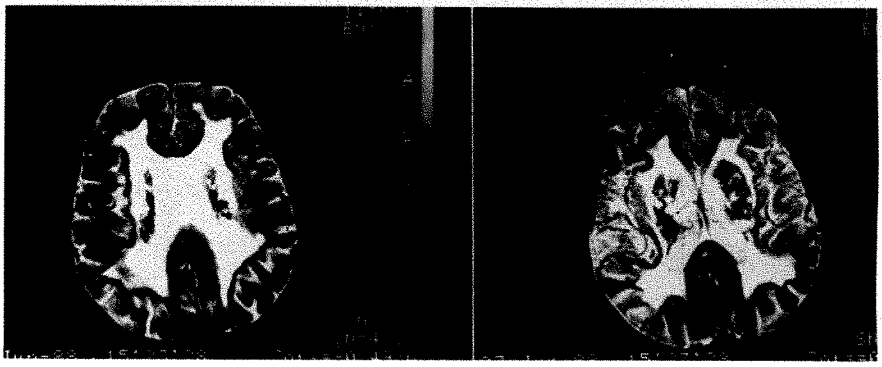


Fig 1.—Cranial T^2-weighted magnetic resonance imaging of patient 1, showing increased signal intensity in the periventricular region.

On examination, he was alert, but mentally slow. Speech, language, and praxis were normal. He could recall one of the three objects at 5 minutes and could not recollect the assassination of any president since his birth. The cranial nerves and reflexes were normal as were sensory examination results. Motor examination revealed normal power, tone, and muscle bulk, but fine finger movements, finger-to-nose, and heel-to-shin testing showed slight uncoordination. His walking was unsteady, without lurching or spasticity.

Laboratory data were normal for VDRL, human immunodeficiency virus antibody, serum cyanocobalamin, folate, urinary and serum arylsulfatase A, long-chain fatty acids, thyroid function tests, sedimentation rate, and antinuclear factor. Also an electromyograph (EMG) and sural nerve biopsy specimen revealed normal results. Cerebrospinal fluid examination showed the following findings: red blood cell count, 1×10^6/L; no white blood cells; protein level, 0.34 g/L; glucose level, 3.16 mmol/L; IgG, 0.03; albumin, 0.15; IgG synthesis, 4.8 mg/d (normal, 0 to 3.1 mg/d); IgG-to-albumin ratio, 0.23 (normal, 0.07 to 0.19); and negative oligoclonal bands. Magnetic resonance imaging showed confluent areas of increased signal in the periventricular regions, mild hydrocephalus, moderate cortical atrophy, and marked atrophy of the corpus callosum. An area of increased signal intensity in the right periventricular region was additionally examined by means of a stereotactic biopsy performed through a frontoparietal approach because of uncertainty regarding the diagnosis.

MATERIALS AND METHODS

Two patients underwent stereotactic brain biopsy, and one patient underwent an open biopsy. In all cases, several fragments of white-tan tissue were obtained. A portion of each specimen was snap frozen in liquid nitrogen for immunohistochemical analysis. The remaining tissue was divided and fixed in 3.75% glutaraldehyde for high-resolution light microscopic and electron microscopic examination or in Hollande's fixative for paraffin embedding.

Stereotactic biopsy was performed on at least three separate coordinates, spanning a total of 30 mm of tissue. The tissue was labeled as within, immediately outside, or remote from the periventricular hyperintense lesion (PHL). The tissue obtained at the time of open biopsy was labeled as periventricular white matter, subcortical white matter, and cortex.

A control group was formed based on review of 154 consecutive patients 18 years old or older who had stereotactic biopsies of radiographically identified lesions performed at the Cleveland (Ohio) Clinic Foundation between June 1987 and November 1989. Nineteen of these 154 patients had nonneoplastic lesions and were selected as control subjects. In these patients, a side-cutting biopsy instrument was used to obtain multiple 10 × 1-mm specimens for frozen section and permanent histopathologic examination. The specimens were processed as mentioned above.

Light Microscopy

Paraffin sections were cut at 5 μm, deparaffinized, and stained with hematoxylin-eosin, congo red, sulfonated alcian blue, crystal violet, Movat's pentachrome, alizarin red, Masson's trichrome, von Kossa's stain, periodic acid-Schiff, modified Kluver-Barrera stain, and Bodian staining.

Electron Microscopy

Tissue specimens for examination by means of high-resolution light microscopy and electron microscopy were fixed in 3.75% buffered glutaraldehyde for 2 hours and postfixed in 1% osmium tetroxide for 2 hours, and then they were embedded in Spurr's epoxy resin. Semithin (1-μm) plastic-embedded sections from all blocks were stained with a mixture of toluidine blue and basic fuchsin. Blocks for electron microscopic examination were selected, and thin sections were cut and subsequently stained with uranyl acetate–lead citrate. At least two blocks per case were examined using an electron microscope (Philips 400 T, Philips Electronics, Einhoven, The Netherlands).

Energy dispersive spectroscopy was performed on brain tissues routinely fixed and processed for electron microscopy as described above. Unstained sections, 60 to 80 nm thick, were mounted on beryllium grids and examined using an electron microscope (Philips 400 T) equipped with a roentgenographic detector and analyzer (EDAX/9100, Edax International Inc, Mahwah, NJ) and operated at 60 kV. Roentgeno-

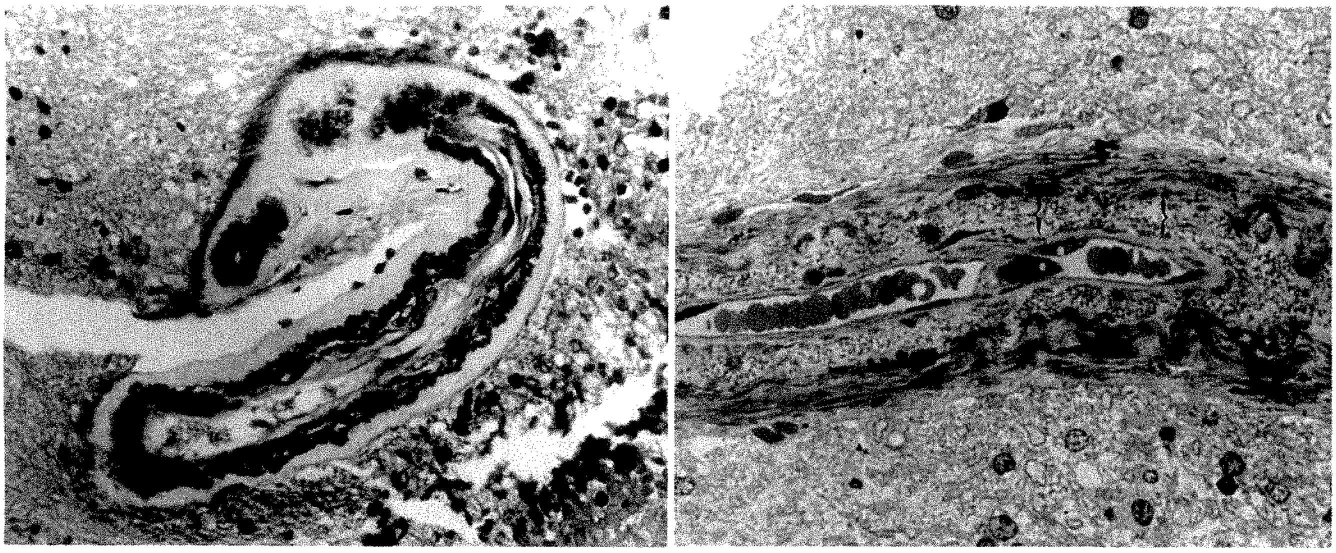


Fig 2.—Case 2. Left, Longitudinal section of a small artery from the deep white matter stained with Movat pentachrome. The normal thickness of the intima can be appreciated. The media is markedly thickened by a mixture of fibrillar connective tissue and black staining material that in this higher magnification photograph is clearly granular (original magnification ×206; final magnification ×540). Right, Longitudinal high-resolution light microscopic plastic section of a small artery from deep white matter stained with a mixture of toluidine blue and basic fuchsin. The intact endothelium and basal lamina can be seen. The medium is thickened and expanded by bundles of collagen that in the inner portion of the medium are randomly oriented and are running in a plane different from those in the outer portion of the medium. Membranous bodies suggestive of secondary lysosomes are present within the media (numerous bodies are enclosed within the braces). The adventitia of cerebral vessels is normally not well developed and cannot be identified in these vessels (original magnification ×160; final magnification ×430).

graphic spectra were accumulated for at least 90 seconds at a count rate of 1000 to 3000 cps, using a take-off angle of 20°.

Immunohistochemistry

Immunohistochemical examination was performed on both frozen and paraffin sections, using the avidin-biotin-complex technique with minor modifications for paraffin-embedded tissue.[10]

Antibodies

Antibodies used for frozen and paraffin sections examined immunohistochemically were as follows: desmin (Dako, Santa Barbara, Calif), glial fibrillary acidic protein (GFP, Dako), *mak*-6 (Triton, Alameda, Calif), vimentin (Dako), IgG, IgA, IgM-κ,-λ, -C3, and -C4 (Becton-Dickinson, Mountain View, Calif), and the amyloid precursor proteins, eg, serum amyloid A component and serum amyloid P component (Vector Laboratories, Burlingame, Calif).

RESULTS

Pathologic Findings

Light Microscopy.—All patients exhibited similar vascular changes. The majority of small vessels (80 to 300 μm) of all types, ie, arterioles, venules, and capillaries, were involved both within the PHL and in the cortex and meninges. In some of them, the vessel wall was strikingly thick and hyalinized (Fig 2, left). Masson's staining demonstrated a thick, concentric band of collagen within the vascular wall. Surrounding this was a clear space that contained variable numbers of convoluted, complex bodies that were variably eosinophilic or basophilic. These bodies were most readily visualized in metachromatically stained plastic sections, where they had the green-blue staining and membranous appearance of large secondary lysosomes (Fig 2, right). Capillaries with adjacent clear spaces and complex bodies, but without expansion of the vessel wall by connective tissue, were identified. In other small vessels, the wall was filled with lipid droplets. Stains for amyloid, including congo red, sulfonated alcian blue, and crystal violet, were negative in all cases, as were alizarin red and von Kossa's stains for calcium. Periodic acid–Schiff staining for glycogen was negative. The endothelium of all vessels was intact and did not appear affected by the process. Movat pentachrome staining demonstrated intact basal lamina and elastic lamina. The vessels were remarkably similar both within the same case and from one case to the next.

Immunohistochemical stains of the affected blood vessels for desmin, glial fibrillary acidic protein, *mak*-6, vimentin, and serum amyloid components A and B were negative. Stains for IgA and IgA-λ were positive in the intima, but not in the vessel wall.

Changes in the surrounding brain tissue were mild. The area corresponding to the PHL had gliosis with mild rarefaction and edema of the white matter. Vacuolization or other changes similar to the perivascular clear spaces were not seen in the surrounding brain tissue. Modified Kluver-Barrera staining demonstrated no demyelination, and Bodian staining revealed no senile plaques or neurofibrillary tangles. Pick bodies were not identified.

Electron Microscopy.—The findings by means of electron microscopic examination were similar in all three cases. The endothelial cells appeared unaffected by the process. The cellular junctions were intact, and the spacing appeared appropriate. Basal lamina and internal elastic lamina beneath the endothelium appeared normal. No inclusion bodies with zebra-body characteristics or other complex structure were observed.

Cells were identified partially surrounding the vessels. These cells had nuclei that conformed to the shape of the vascular wall and were partially invested with basal lamina. Within the cytoplasm of the cells were multiple large complex lysosomes, and numerous

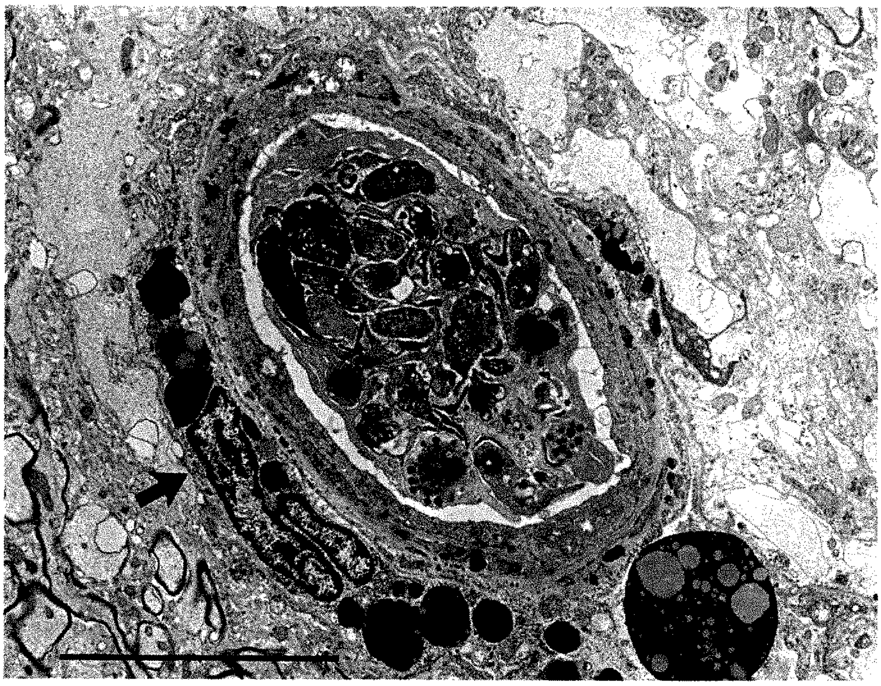
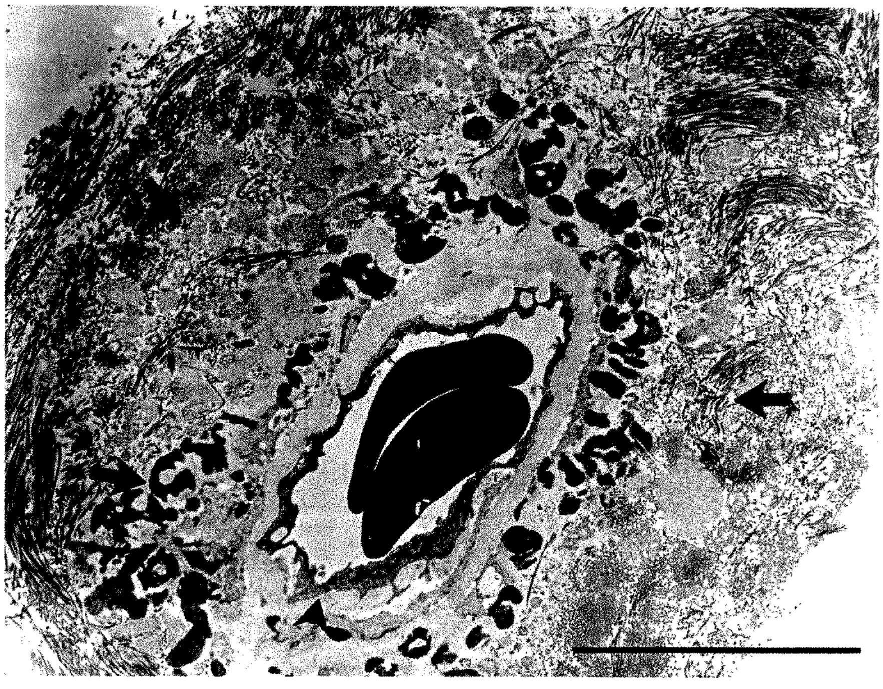


Fig 3.—Case 2. Electron micrograph of a cross-section of vessel double stained with uranyl acetate–lead citrate. A thrombus is seen within the lumen. Cells containing complex lysosomes and lipid are seen conforming to the vascular wall (arrow). The cells are at least partially invested with basal lamina. It is difficult to identify them unequivocally as either pericytes or macrophages. Bar indicates 10 μm.

Fig 4.—Case 2. Electron micrograph of a cross-section of a small artery double stained with uranyl acetate–lead citrate. The endothelium and basal lamina appear intact (arrowhead). The remainder of the arterial wall, including all media and possibly the adventitia, is replaced by fragments of collagen, elastin, basal lamina, and granular electron-dense material (arrows). Bar indicates 10 μm.



large lipid droplets (Fig 3). Similar lysosomes were seen in cells that were separated from the vessel by a clear space. These latter cells had rounded nuclei and cytoplasmic filaments, and they were not invested by vascular basal lamina. The identity of either cell type was not clear; they could be pericytes, macrophages, glial cells, or all three.

The medium of these vessels was markedly thickened by layers of mature collagen mixed with fragments of elastin, basement membrane, and granular electron-dense extracellular material (Figs 4 and 5). The overall impression was that of a disorganized medial layer. Roentgenographic energy dispersive spectroscopy of this granular material and of the lysosomes indicated lack of metallic or mineral components. The entire thickness of the medium was involved. Smooth-muscle cells were absent and seemed to have been replaced by connective tissue or by lipid.

Many of the vessels were surrounded by swollen astrocytic foot processes containing filamentous material. These swollen processes correlated with the clear spaces noted by light microscopy. Splitting of the myelin lamellae was focally present.

Electron microscopic examination confirmed that the thickened vascular walls were composed of collagen, elastin fragments, basal lamina, and electron-dense material, or lipid. No amyloid or intermediate filaments were visualized by electron microscopy. Glycogen was not part of the thickened vascular wall as demonstrated by the negative periodic acid–Schiff staining. Findings by means of energy dispersive spectroscopy, special stains for calcium (alizarin red and von Kossa's stain), and immunohistochemical examination indicated that the extracellular granular electron-dense material was not mineral or metallic, glycogen, or immunoglobulin.

Diagnoses of the 19 patients in the control group (mean age, 38 years) who had nonneoplastic disease are summarized in the Table. No patient had vascular changes similar to those identified in our three patients.

COMMENT

Our three patients had similar clinical and radiological features, including progressive dementia, abnormal gait, spasticity (two patients), urinary incontinence (two patients), preservation of sensory modalities, confluent PHL identified on MRI, and mild ventricular enlargement. The pathological features of the PHL seen on MRI were characterized by gliosis with mild rarefaction and edema of the white matter and a predominantly white matter vasculop-

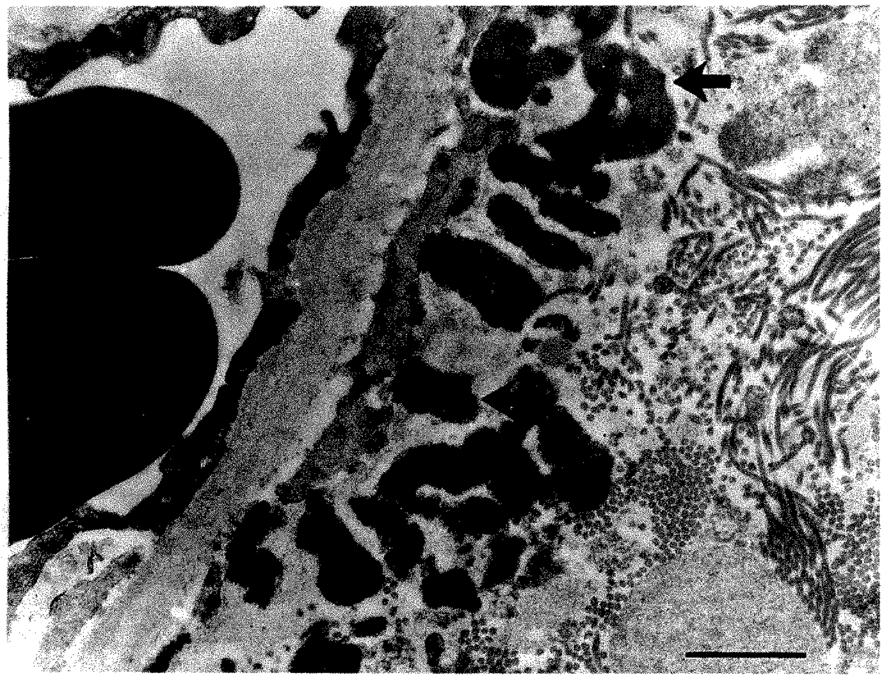


Fig 5.—Case 2. A high-magnification electron micrograph of the granular electron-dense deposits double stained with uranyl acetate–lead citrate. These deposits are osmiophilic and are present in basal lamina beneath the endothelium, as well as admixed with the adjacent connective tissue (arrows). The aggregates are of no particular shape or size, and they are not present within endothelium cells or within the vascular lumen. Bar indicates 1 μm.

Diagnoses Established by Stereotactic Biopsy in Control Patients

Diagnosis	No.
Anoxic encephalopathy	1
Cerebritis	1
Encephalitis	1
Hamartoma	2
Hematoma (thrombosed)	1
Lymphomatoid granulomatosis	1
Multiple sclerosis	3
Pick's disease	1
Progressive multifocal leukoencephalopathy	3
Radiation necrosis	1
Thrombosed arteriovenous malformation	1
Vasculitis	3
Total	**19**

athy involving arterioles, capillaries, and venules. The vasculopathy was characterized on light and electron microscopy by three main features: (1) thickening of the vascular media by a disorganized mixture of collagen, elastin fragments, basement membrane, lysosomes, and granular electron-dense material or lipid that had replaced the medial smooth-muscle cells; (2) perivascular cells, of uncertain identity, containing multiple large complex lysosomes and lipid within their cytoplasm; and (3) swollen astrocytic foot processes surrounding the involved vessels. These changes were present in all three patients. None of our patients showed any abnormalities of intima. Specifically, there was no evidence of atherosclerosis or vasculitis such as intimal thickening, focal deposition of lipid, lipohyalinosis, or fibrinoid necrosis. There was no evidence of amyloidosis or of a proliferation or deposition of intermediate filaments.

The differential diagnosis in these three patients includes Alzheimer's disease, the most common cause of dementia that may be associated with PHL identified on MRI.[11] Although we cannot completely exclude Alzheimer's disease on the basis of the limited tissue available for pathological examination, the young age of the patients; the lack of prominent aphasia, agnosia, and apraxia despite progressive dementia; the early motor signs; and the presence of the vasculopathy argue strongly against this diagnosis. Another diagnostic possibility is normal pressure hydrocephalus; however, the early onset, the absence of diseases predisposing to meningeal fibrosis, and the asymmetry of motor findings and prominent spasticity in two patients argue against diagnosis. Furthermore, normal pressure hydrocephalus would not explain the pathological findings and the strokelike episodes seen in two of our three patients. Other diseases associated with dementia and PHL identified on MRI that were excluded by clinical, laboratory, or pathological studies include multiple sclerosis, the leukodystrophies, human immunodeficiency virus infection, toluene exposure,[12] and progressive multifocal leukoencephalopathy.

The strokelike episodes and focal motor findings in two of our three patients suggest a vascular origin. None of the patients had cardiac disease or occlusive large-vessel cerebrovascular disease. This suggests that the small-vessel vasculopathy, which was not present in any of our age-matched control patients, was the likely cause of clinical and radiological features in our patients.

Although the clinical and radiological features of our three patients resemble those in patients with BSAE,[1-7] important differences exist. Typically, patients with BSAE are elderly and hypertensive, whereas our patients were middle-aged, and none of them had sustained hypertension. Furthermore, the vascular pathologic features in our patients were different from the vascular changes seen in patients with BSAE, which consist primarily of lipohyalinosis of small arterioles in the deep white matter.[8,9]

There are accumulating epidemiologic and pathologic data to suggest that a large subgroup of PHLs identified on MRI have a vascular origin.[13-15] Risk factors consistently associated with these lesions are old age, hypertension, and ischemic stroke. Pathologically, PHLs are characterized by dilated perivascular spaces surrounding hyalinized, sclerotic, and ectatic vessels; gliosis; and myelin pallor.[13,16,17] Occasionally, areas of cystic infarction are also identified.[18] A commonly proposed theory is that PHLs identified on MRI are caused by subcortical ischemia as a consequence of subcortical occlusive small-vessel disease, perhaps in association with low cerebral blood flow.[13-15] If this theory is true, it is likely that several etiologic subtypes of small-vessel disease may cause these lesions. Indeed, periventricular lesions have been described in patients with poorly controlled hypertension,[14] amyloid angiopathy,[19,20] and mitochondrial angiopathy.[21-24]

The cause of the vasculopathy remains unclear. The complex lysosomes seen in the vessel walls in our patients have been previously described[25] as the result of intoxication with a variety of drugs, but a history of drug abuse was only elicited in one of our patients. No common therapeutic drug was used by all three patients. The electron-dense material seen in the vessel walls is not amyloid, immunoglobulin, intermediate filament, or a glycoprotein. However, the fact that the granular material was identified on the endothelial side of the basal lamina beneath intact endothelial cells and junctions suggests the possibility that this material was transported from the vascular lumen.

Further studies are necessary to clarify the spectrum of vasculopathies associated with dementia and PHLs identified on MRI.

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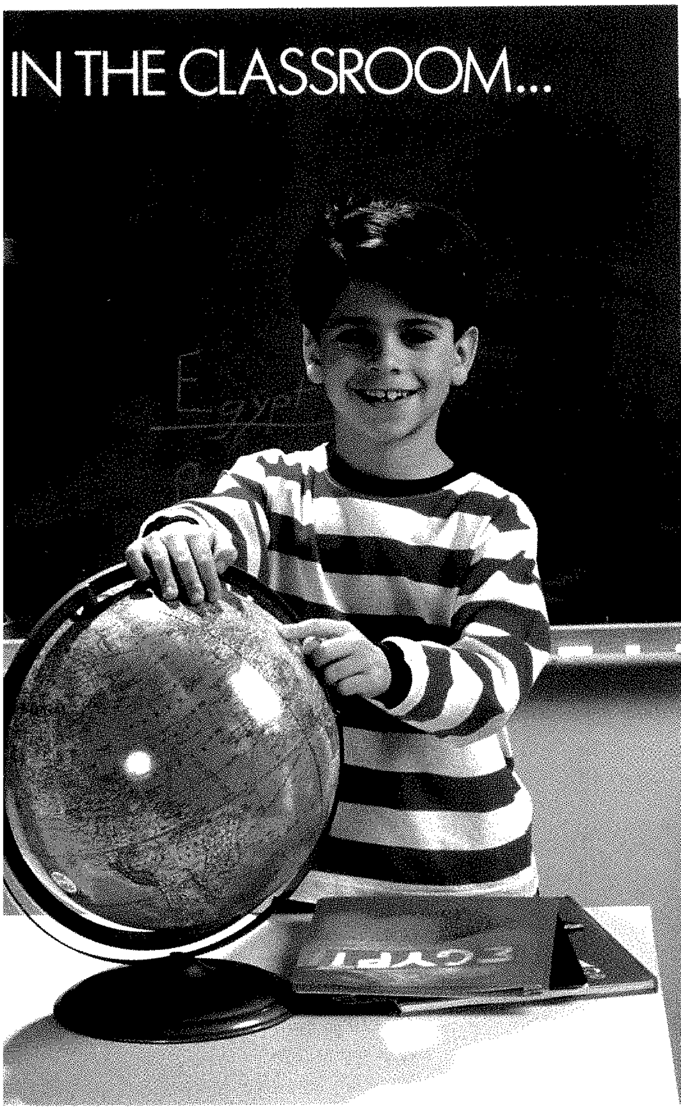
References

1. Binswanger O. Die Abgrenzung der algemeinen progressiven Paralyse. *Berl Klin Wochenschr.* 1894;31:1103-1105, 1137-1139, 1180-1186.
2. Olszewski J. Subcortical arteriosclerotic encephalopathy: review of the literature on the so-called Binswanger's disease and presentation of two cases. *World Neurol.* 1962;3:559-575.
3. Caplan LR, Schoene WC. Clinical features of subcortical arteriosclerotic encephalopathy (Binswanger's disease). *Neurology.* 1978;28:1206-1215.
4. Babikian V, Ropper AH. Binswanger's disease: a review. *Stroke.* 1987;18:2-12.
5. Golo R, Ishii N, Fukasawa H. Diffuse white matter disease in the geriatric population. a clinical, neuropathological, and CT study. *Radiology.* 1981;141:687-695.
6. Rosenberg GA, Kornfeld M, Stovring J, Bicknell JM. Subcortical arteriosclerotic encephalopathy (Binswanger): computerized tomography. *Neurology.* 1979;29:1102-1106.
7. Kinkel WR, Jacobs L, Polachini I, Bates V, Heffner RR. Subcortical arteriosclerotic encephalopathy (Binswanger's disease): computed tomographic, nuclear magnetic resonance, and clinical correlations. *Arch Neurol.* 1985;42:951-959.
8. Burger PC, Burch JG, Kunze V. Subcortical arteriosclerotic encephalopathy (Binswanger's disease). *Stroke.* 1976;7:626-631.
9. DeReuck J, Crevits L, DeCoster W, et al. Pathogenesis of Binswanger chronic progressive subcortical encephalopathy. *Neurology.* 1980; 30:920-928.
10. Hsu S, Raine L, Fanger H. The use of antiavidin antibody and avidin-biotin-peroxidase complex in immunoperoxidase technics. *Am J Clin Pathol.* 1981;75:816-821.
11. Fazekas F, Chawluck JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5T in Alzheimer's dementia and normal aging. *AJNR.* 1987;8:421-426.
12. Filley CM, Heaton RK, Rosenberg NL. White matter dementia in chronic toluene abuse. *Neurology.* 1990;40:532-534.
13. Chimowitz MI, Awad IA, Furlan AJ. Periventricular lesions on MRI: facts and theories. *Stroke.* 1989;20:963-967.
14. Awad IA, Spetzler RF, Hodak JA, et al. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, I: correlation with age and cerebrovascular risk factors. *Stroke.* 1986;17:1084-1089.
15. Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurement and cerebrovascular risk factors. *Stroke.* 1988;19:1285-1288.
16. Awad IA, Johnson P, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, II: postmortem pathological correlation. *Stroke.* 1986; 17:1090-1097.
17. Braffman BH, Zimmerman RA, Trojanowski JQ, et al. Brain MR: pathologic correlation with gross histopathology, II: hyperintense white matter foci in the elderly. *AJNR.* 1988;9:629-636.
18. Marshall VG, Bradley WG, Marshall CE, Bhoopat T, Rhodes RH. Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology.* 1988;167:517-522.
19. Gray F, Dubas F, Roullet E, Escourolle R. Leukoencephalopathy in diffuse hemorrhagic cerebral amyloid angiopathy. *Ann Neurol.* 1985;18:54-59.
20. Janota I, Mirsen TR, Hachinski VC, Lee DH, Merskey H. Neuropathologic correlates of leuko-araiosis. *Arch Neurol.* 1989;46:1124-1128.
21. Sakuta R, Nonaka I. Vascular involvement in mitochondrial encephalopathy. *Ann Neurol.* 1989;25:594-601.
22. Morgan-Hughes JA, Hayes DJ, Clark JB, et al. Mitochondrial encephalopathies: biochemical studies in two cases revealing abnormalities in the respiratory chain. *Brain.* 1982;105:553-582.
23. Lach B, Preston D, Servidei S, et al. Maternally inherited mitochondrial encephalomyopathy: a vasculopathy. *Muscle Nerve.* 1986;9:180.
24. Ohama E, Ohara S, Tanaka K, et al. Mitochondrial angiopathy in cerebral blood vessels of mitochondrial encephalomyopathy. *Acta Neuropathol (Berl).* 1987;74:226-233.
25. Estes ML, Ewing-Wilson D, Chou SM, et al. Chloroquine neuromyotoxicity: clinical and pathologic perspective. *Am J Med.* 1987;82:447-455.

Seizures controlled, thoughts clear, smiles bright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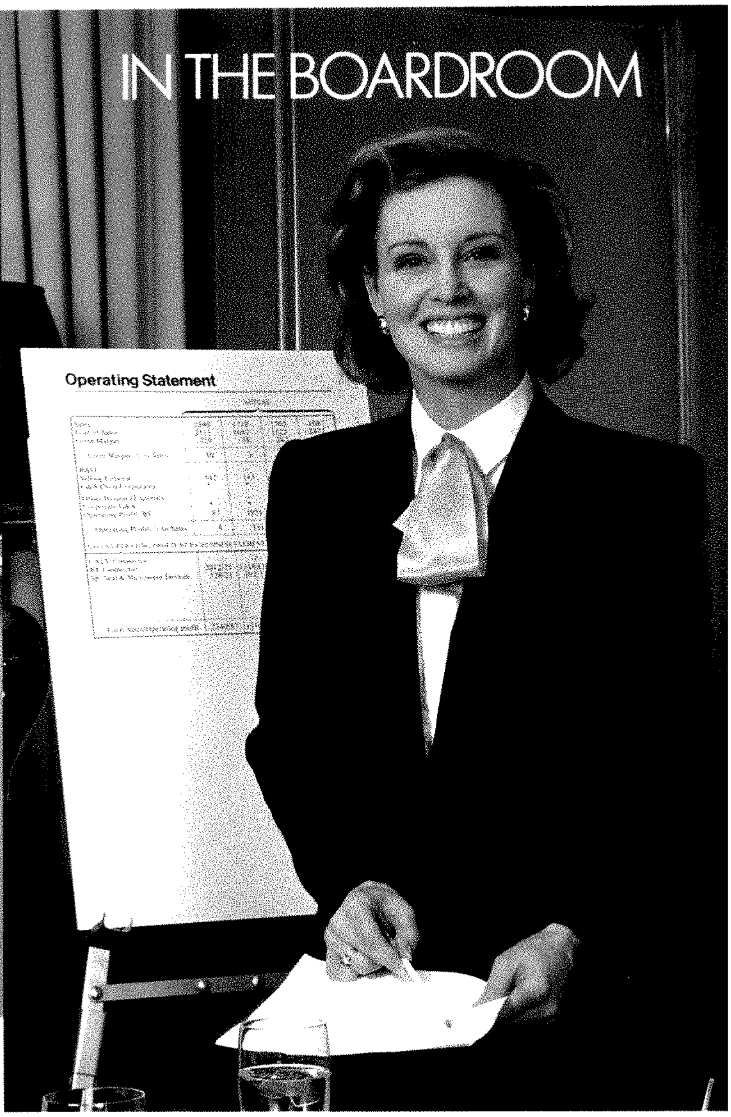

Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

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Tegretol®

carbamazepine USP

200-mg scored tablets
100-mg chewable tablets

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References

1 Smith DB, Mattson RH, Cramer JA, et al Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone *Epilepsia* 1987;28(suppl 3):S50-S58.

2 Mattson RH, Cramer JA, Collins JF et al Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures *N Engl J Med* 1985;313:145-151

3 Herranz JL, Armijo JA, Arteaga R Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children *Epilepsia* 1988;29:794-804

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink Tablets of 200 mg—pink

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW. APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA

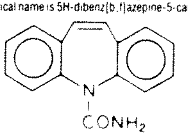
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY NONETHELESS. COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only)

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 µg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 µg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types

1 Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types

2 Generalized tonic-clonic seizures (grand mal)

3 Mixed seizure patterns which include the above, or other partial or generalized seizures

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General)

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia

Beneficial results have also been reported in glossopharyngeal neuralgia

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported

Tegretol has shown mild anticholinergic activity, therefore, patients with increased intraocular pressure should be closely observed during therapy

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE)

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used

Thyroid function tests have been reported to show decreased values with Tegretol administered alone

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1, talipes, 1, anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women

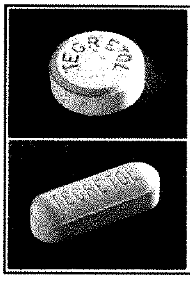
It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established



Only TEGRETOL.
brand of carbamazepine.
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

Hemopoietic System. Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria

Skin. Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary

Cardiovascular System. Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds

Liver. Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis

Respiratory System. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia

Genitourinary System. Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown

Nervous System. Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established

Digestive System. Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes

Musculoskeletal System. Aching joints and muscles, and leg cramps

Metabolism. Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests)

Other. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman), children, 10 g (6-year-old boy), small children, 5 g (3-year-old girl)

Oral LD50 in animals (mg/kg): mice, 1100-3750, rats, 3850-4025, rabbits, 1500-2680, guinea pigs, 920

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested

Respiration. Irregular breathing, respiratory depression

Cardiovascular System. Tachycardia, hypotension or hypertension, shock, conduction disorders

Nervous System and Muscles. Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia

Gastrointestinal Tract. Nausea, vomiting

Kidneys and Bladder. Anuria or oliguria, urinary retention

Laboratory Findings. Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias

Combined Poisoning. When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote

Elimination of the Drug. Induction of vomiting

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol

Measures to Reduce Absorption. Activated charcoal, laxatives

Measures to Accelerate Elimination. Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children

Respiratory Depression. Keep the airways free, resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen

Hypotension, Shock. Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered

Convulsions. Diazepam or barbiturates

Warning. Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week)

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days

Treatment of Blood Count Abnormalities. If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance***: Adjust dosage to the minimum effective level, usually 800-1200 mg daily

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance***: Adjust dosage to the minimum effective level, usually 400-800 mg daily

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C)

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak®—One Unit	
12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 0028-0027-61

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet

Protect from moisture

Dispense in tight container (USP)

Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles

Printed in U.S.A. C90-34 (Rev 6/90)

Geigy
GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

Regional Cerebral Blood Flow Correlates of Language Processes in Reading Disability

D. Lynn Flowers, PhD; Frank B. Wood, PhD; Cecile E. Naylor, PhD

• **This series of studies tests the hypothesis of abnormal left hemisphere activation in reading-disabled subjects during language task performance. First, a left superotemporal focus of activation, as measured by regional cerebral blood flow, was found to be positively correlated with task accuracy in a group of 69 normal adults. Next, that left superotemporal activation was replicated in a second group of 83 adults whose childhood reading ability was known from standardized tests given in childhood. Finally, in that latter group, childhood reading ability was also found to be inversely correlated with focal activation in a more posterior, temporoparietal area of cortex. Adult reading outcome was statistically unrelated to this finding. The results are interpreted as suggesting a trait anomaly of left hemisphere cerebral activation in adults who were dyslexic as children and as providing an existence proof of individual differences in focal cortical activation sites during constant task demands.**

(*Arch Neurol.* 1991;48:637-643)

Dyslexia or reading disability, defined as the failure to achieve age-predicted reading levels despite normal intelligence and adequate learning opportunity, has triggered numerous theoretical explanations. However, inasmuch as persistent language deficits are consistently found,[1-4] a left hemisphere neural anatomical substrate has been proposed especially often for developmental reading disability.[5]

Chronic atypical left hemisphere organization in dyslexic individuals is suggested by two types of anatomical evidence. First, at the microscopic level, neuronal anomalies including dysplasias in the cortical layers and ectopic neuronal cell bodies have been observed in human dyslexics. In contrast with findings in normal readers, consecutively presenting dyslexic patients were all found by Galaburda and others[6-8] to have neural anomalies, predominantly in the left perisylvian cortex. These abnormalities are proposed to occur in the second trimester during the wave of cell migration that forms the upper cortical layers. Similar anomalies can be induced in laboratory animals by creating small necroses in the cortex, thus interrupting cells as they migrate into the superficial cortical layers.[9] In humans, a specific necrotic agent has not been identified, but a slower maturation rate of the left hemisphere temporal region is proposed to render it especially vulnerable to insult during this period of migration.[5]

Second, at the macroscopic level, atypical neural organization in reading-disabled subjects is suggested by the absence of the normal left-greater-than-right asymmetry in the posterotemporal planum in autopsy material.[6,7] Studies using in vivo techniques, computed tomography, and magnetic resonance imaging also have reported temporal planum symmetry or reversed asymmetry statistically more often in language-disabled subjects.[10,11] A possible origin is anomalous cell migration and organization, demonstrated experimentally in primate studies[12,13]: in the fetal monkey, after a unilateral frontal lesion, greater-than-normal neural projections are found bilaterally. The responsible mechanism is believed to be reduced cell death during corticogenesis. In the case of reading disability, the more symmetrical temporal planum might then also result from an original unilateral lesion, possibly in the left hemisphere.

Thus, there is reason, from microstructural and gross structural studies, to consider that the behavioral deficit observed in developmental reading disability may be related to the anomalous organization of tissue lying within the left hemisphere processing regions.

In addition, physiological evidence suggests that verbal processing deficits are related to atypical neural activity. The intraoperative brain stimulation mapping technique has shown that sites functionally involved with basic language skills (for instance, naming, orofacial sequencing, and phonetic discrimination) are distributed along the sylvian fissure.[14,15] In a group of epileptic patients with left hemisphere dominance for language, greater variability in the distribution of language functions was reported than would be predicted by the classic models. The extent of epileptogenic tissue did not predict this variability, but verbal ability did. That is, patients with poorer verbal ability demonstrated more naming interruptions in response to inferoparietal (angular gyrus) stimulation, a significant posterior shift from the left temporal site that was activated in patients with higher verbal ability.

Based on these findings, Ojemann and Whitaker[16] have speculated that displaced representation of a core language function from the posterotemporal area into the nearby parietal region might be typical of those with poorer verbal ability. They have ob-

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served that early left anterotemporal lesions result in wider representation of naming in the posterotemporal and parietal cortex. Functional displacement of some temporal lobe language mechanisms to the surrounding parietal cortex, the extent of which is related to how much the lesion encroaches on language centers, also has been proposed by Rasmussen and Milner[17] to occur postnatally following early brain insult. Translocalization of function into nearby cortical areas following experimental lesions is also known to occur in young, nonhuman primates.[18,19]

Table 1.—Descriptive Measures for 69 Normal Subjects*

Variable	Mean ± SD	Range
Age, y	29.8 ± 7.5	18-46
Education, y	14.9 ± 2.2	12-25
Task accuracy (d′)	4.8 ± 1.1	1.9-6.0
Anxiety score	56.3 ± 11.3	40-91
Estimated Full-Scale IQ	108.6 ± 12.0	92-146
Estimated Verbal IQ	107.1 ± 13.2	88-150
Estimated Performance IQ	108.7 ± 11.2	87-139

*Anxiety Score is the sum of the pretest and posttest scores on the Spielberger State-Trait Anxiety Inventory (n = 47). Estimated IQ scores are extrapolated from two Verbal subscales (Vocabulary and Digit Span) and two Performance subscales (Block Design and Digit Symbol) of the Wechsler Adult Intelligence Scale-Revised.

Table 2.—Descriptive Measures for 83 Orton Group Subjects by Childhood Reading Level*

	Reading Disabled (n = 33)	Borderline (n = 27)	Nondisabled (n = 23)
Age, y	33.8 ± 5.7	33.8 ± 4.3	32.2 ± 5.3
Education, y†	14.7 ± 2.6	16.3 ± 2.3	17.2 ± 1.6
Task accuracy d′‡§	3.04 ± 1.0	3.93 ± 1.1	4.88 ± 0.9
State anxiety score	61.3 ± 11.8	63.6 ± 15.4	57.7 ± 10.6
Childhood IQ			
Full-Scale‡	102.5 ± 10.6	108.5 ± 11.1	119.0 ± 6.5
Verbal‡	98.5 ± 12.0	107.4 ± 11.5	119.3 ± 8.9
Nonverbal‖	106.4 ± 11.3	108.2 ± 12.5	114.8 ± 8.3
Adulthood IQ			
Full-Scale†	96.0 ± 11.0	105.0 ± 12.3	110.8 ± 11.8
Verbal‡	94.5 ± 11.0	103.2 ± 10.9	112.7 ± 10.8
Nonverbal	99.7 ± 11.4	106.0 ± 12.9	106.2 ± 12.5

*Values are mean ± SD.

†Reading-disabled subjects differ from all others by Tukey's Studentized Range Test at $P < .05$.

‡All paired comparisons are significantly different.

§Nondisabled readers do not differ significantly from subjects in the normal (study 1) group.

‖Reading-disabled and borderline subjects differ from good readers.

PHYSIOLOGICAL MEASUREMENTS

Of the noninvasive physiological measures available for study of nonclinical subjects, the xenon 133 regional cerebral blood flow (rCBF) method is well suited for monitoring the neural correlates of sustained language functions. Its temporal window is on the order of a few minutes, its relative safety and low cost allow the use of large normal reference groups and multiple conditions,[20,21] and its ability to resolve gray- vs white-matter flow exceeds that of other methods.

Only two rCBF studies of dyslexic adults have been published to date. The first[22] compared two severely impaired male subjects with age-matched male subjects of normal reading ability while they read a prose story silently. A second study[23] compared a group of 14 dyslexic male subjects with normal subjects on a semantic classification task. Neither study concluded that dyslexic subjects had a left hemisphere verbal processing deficit. Definitive conclusions cannot be drawn from these studies, however: the sample sizes were too small to control statistically for trait and state individual differences due to age, IQ, and anxiety; and activation tasks were not closely related to those particular language mechanisms involved in reading disability.

In this study, an orthographic task was used, since persisting spelling deficit is often found to characterize adults with reading disability histories, even when their oral reading has improved.[24]

Clearly, it is also desirable to study a large sample of adults whose childhood reading and academic histories are fully documented. Such a population was available for this investigation. The great advantage of using this population was that the diagnosis of reading disability could be made based solely on objective childhood reading tests, which could then be used to predict adult blood flow patterns elicited by cognitive tasks. Thus, regardless of adult accomplishment due to training or practice, a hypothesis of neural physiological deficiency rooted in early development could be tested in subjects defined by their documented childhood reading disability.

THEORETICAL PREDICTIONS

From the studies of Ojemann and coworkers and related evidence, it was plausible to predict that (1) in a normal, nonclinical population, a language-based task would be accompanied by focal activation of the left hemisphere perisylvian (superotemporal) regions; and (2) in an adult population that included subjects with documented childhood reading impairment, displacement or spread of activation to surrounding regions, in particular to the adjacent posterior (temporoparietal) region, would be related statistically to the degree of early disability.

Three studies utilizing the rCBF method are reported herein. The first involves orthographic task accuracy correlation with blood flow during the task in healthy adults with no history of reading problems; the second replicates the same correlation in a group of adults with documented, varied reading histories; and the third is a prediction from childhood reading level of adult blood flow as measured during task activation.

SUBJECTS AND METHODS

Subjects

The three studies reported shared the same equipment, stimuli, and procedure but utilized different sets of subjects. Experimental procedures and safety factors were explained to subjects and informed consent was obtained.

For study 1, a normal sample of 69 subjects (39 men and 30 women) performed an orthographic analysis task. All subjects were right-handed and of average intelligence (Wechsler Adult Intelligence Scale–Revised[25]; Table 1). An interview determined that no subject had a history of reading remediation or had repeated grades.

The 83 subjects (72 men and 11 women) in studies 2 and 3 were referred to the Orton Reading Center in Winston-Salem, NC, during its operation between 1957 and 1972. Their childhood records, accessed with written permission, are maintained at the Health Sciences Library of Columbia University, New York, NY. These records contain detailed parent and teacher interviews, school reports, and scores on standardized reading, achievement, and IQ tests. Variables used to control statistically for subject differences are given in Table 2.

Childhood and adult intellectual ability was assessed using standardized tests appropriate to the age range.[25,26] All subjects had childhood and adult IQ scores of at least 80 on either the Verbal or the Performance scale.

Subjects who had attended the Orton Reading Center were assigned to reading levels based on childhood reading ability using the Reading Quotient (RQ) according to the following formula:[27] RQ = (Reading Age/Chronological Age) × 100. "Reading age" is defined as the reading grade level plus 5, determined by an oral reading test (either the Gray Oral Reading Test[28] or the reading portion of the Wide Range Achievement Test [WRAT][29]). If both of the two oral reading quotients were 82 or less, a subject was said to be reading disabled (n = 33). If both quotients were above 91, then the subject was classified as not reading disabled (n = 23). All those not meeting these stringent criteria were classified as borderline (n = 27). The cutoff scores were chosen to represent local school guidelines for learning-disabled classification when recruited, ie, a diagnosis of reading disability is equivalent to being at least 1.5 years behind the reading grade level at the beginning of the third grade.

For the Orton Reading Center group, two criteria defined current (adult) reading level: scores on the WRAT-Revised (WRAT-R)[30] and a reading discrepancy score (difference between the actual reading level on the Gray Oral Reading Test and the expected reading level as calculated using the formula of Finucci et al[31]). Cutoff scores of 82 and 91 on the WRAT-R and −1.2 and −0.6 discrepancy on the Gray scores were set.

All subjects were free of known neurological impairment, major psychopathological conditions, hearing or other sensory impairment, and chronic pulmonary dysfunction. Handedness in the Orton Reading Center group was assessed by a self-report inventory.[32] Seven were left-handed and six were ambidextrous.

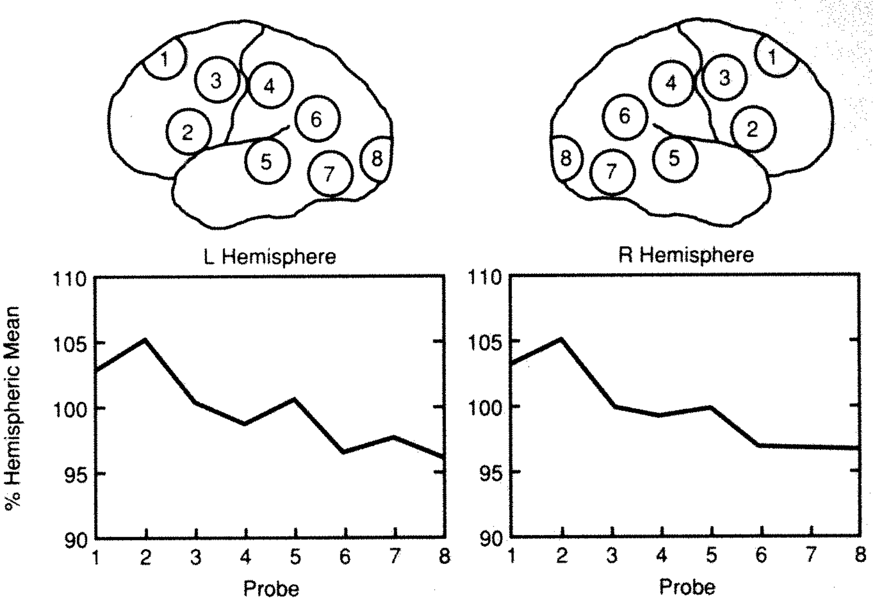

Fig 1.—Hemispheric mean corrected values as a function site for 69 normal subjects. Probe locations: 1, frontal eye fields; 2, Broca's area; 3, hand motor; 4, hand sensory; 5, Wernicke's area; 6, temporoparietal area; 7, inferior temporo-occipital; and 8, primary occipital.

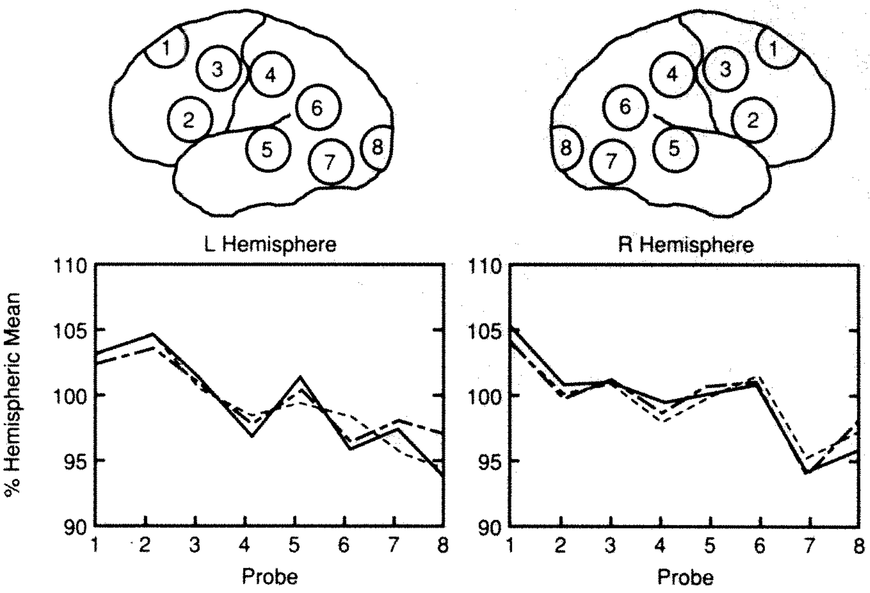

Fig 2.—Hemispheric mean corrected values plotted as a function of probe sites in the left and right hemispheres of 83 subjects from the Orton Reading Center subject pool by childhood reading classification. Dotted line indicates reading disabled (n = 33); dashed-and-dotted line, borderline (n = 27); and solid line, not reading disabled (n = 23). Probe locations are as in Fig 1.

Equipment

Regional cerebral blood flow was measured by a Novo Cerebrograph 32C system (Novo Diagnostic Systems, Bagsvaerd, Denmark), which dispensed the radioactive tracer (^{133}Xe), collected expired air, and measured gamma emissions from the head in 5-second bins. A minicomputer (PDP-11, Digital Equipment Corp, Maynard, Mass) gave a continual on-line numeric and graphics display of the technical quality of ongoing measurements. Signals warned of carbon dioxide and oxygen level abnormalities. A highly sensitive leak detector monitored leakage from the face mask; a soft plastic device fitted over the subject's nose and mouth to collect expired air. The subject was allowed to adapt and breathe normally.

For each measurement, a mixture of air and concentrated ^{133}Xe (approximately 25.9×10^4 Bq/L of air) was administered for 1 minute while clearance was measured by 16 thallium-activated sodium iodide crystal scintillation detectors mounted in shielded lead collimators, eight on each hemisphere. Sites were chosen to represent primary sensory areas, language regions, and frontal regions thought to be involved in attentional processes. Correct placement of the detectors was assured by matching markers on the helmet to anatomical landmarks. This method had been previously verified using both roentgenogram and cadaver checks.[33]

The Initial Slope Index (ISI) of Risberg et al,[34] a conservative index of gray-matter activity, represents the flow at each probe site. A value for each probe site is calculated from the clearance rate of radioactive tracer at each probe site, beginning when saturation has declined to 20% of its maximum level and continuing over the next minute. The balance of time to the end of the 11-minute measurement period serves to calculate corrections for clearance from nonneural tissue.

Procedures

Subjects performed three tasks, appropriately counterbalanced, involving verbal memory, auditory perception, or spelling analysis. Only results from the spelling task are reported herein.

With the room quiet and darkened, task and tracer delivery were begun simultaneously. Subjects listened to 88 highly imageable, common concrete nouns taken from a standard list[35] and delivered binaurally through ear insert phones (Lanier Worldwide, Atlanta, Ga) via a Dolby cassette recording played on a receiver (Realistic SCR-2500, Tandy Corp, Fort Worth, Tex). Half of the words were exactly four letters long, and these were randomly distributed in the list. The words were delivered at 2.5-second intervals, the entire task taking 3 minutes 40 seconds. Subjects were instructed to make a bimanual finger-lift response to any four-letter word. Hits and false alarms were recorded. Twenty minutes was allowed between tasks.

RESULTS

Following common rCBF practice, each of the 16 ISI values obtained from each subject was corrected by that subject's hemispheric mean flow: (ISI/Mean Flow) × 100. A general linear model related these hemisphere-corrected ISIs either to accuracy of task performance or to childhood reading level. Childhood IQ was included in the model as a covariate to assure that predicted differences in flow were not due to differences in general ability. Also, since the rCBF literature has consistently shown the independent effects of age, gender, and task order on blood flow,[36-39] these variables were entered as covariates in the general linear model predicting flow from task accuracy. Although all 16 probe values could be subjected to post hoc statistical analysis, the hypothesis that perisylvian language areas would be activated by task identifies two a priori sites: the inferior posterofrontal premotor area of Broca (probe 2) and the superior posterotemporal area of Wernicke (probe 5).

Task accuracy was calculated as d', to reflect both hits and false alarms.[40] Mean (±) d' values for the normal and Orton Reading Center groups were 4.8 ± 1.1 and 3.8 ± 1.2, respectively, indicating that the target stimuli were generally well discriminated by all subjects.

Study 1

The rCBF profile of hemisphere corrected ISI values for the 69 normal subjects, plotted by hemisphere and probe sites, is shown in Fig 1. By inspection, the pattern of activation is one of "hyperfrontality" typically seen in normal, comfortably alert subjects,[41] ie, a generally symmetrical profile with greater activation in the frontal as compared with posterior areas. The left temporal site also was somewhat elevated above its neighbors during this auditory verbal task.

Accuracy of task performance was positively correlated with blood flow only at the left Wernicke's area (probe site 5; F[1,63]=4.14, $df=1,63$, $P<.05$) but not at the left Broca's area (probe site 2; $P>.10$) or at any other probe site. The general linear model analyses statistically controlled for differences in flow that might be accounted for by a subject's age, full-scale IQ score, gender, or the influence of task order (ie, whether the task was first, second, or third in a series); none of these variables were confounded with the significant effect in Wernicke's area. In a subset of 47 subjects who completed subjective inventories of state anxiety,[42] statistical control for state anxiety also did not change these relationships.

Therefore, the hypothesis was confirmed for the temporal lobe site: in this normal subject group, accuracy on a spelling-related task was related to focal activation of one left perisylvian region, Wernicke's area. While this finding does not specify which features of accurate task performance evoked the Wernicke's area response, it is apparent that some readily measurable trait and state correlates of task performance, such as IQ and anxiety, were not responsible for the temporal lobe activation.

Study 2

Regional cerebral blood flow values at all probe sites were evaluated but, based on the findings from the normal subject group, it was hypothesized a priori that task d' would predict activation only at the left Wernicke's area (probe 5). Indeed, task performance did predict the rCBF measure at Wernicke's area (F[1,77]=7.22, $P<.01$). In addition to age, IQ, gender, and task order, already statistically accounted for in the analysis, self-reported educational attainment, state anxiety, or handedness as controlling variables also did not change the relationship. Thus, the hypothesized relationship between neural activation of the posterior left hemisphere language area and performance of a spelling task, found first in a normally presenting, nonclinical population, was strongly replicated in a second group of subjects whose childhood reading ability ranged from severely impaired to normal. Task performance was not related to flow at any other site.

Study 3

The rCBF profiles for the Orton Reading Center subjects, plotted by childhood reading level, are shown in Fig 2. The poor readers exhibited a reduced response in Wernicke's area, compared with good readers. That is not surprising, since poor readers performed the task less well, and task performance was shown in study 2 to correlate with Wernicke's area flow.

The hypothesis was that in a group of adults with varied, documented reading histories, the poorer the childhood reading level was, the more likely it was that task-related cortical activation would be accompanied by activation elsewhere than in the temporal lobe language-processing areas. Specifically, given the findings from brain stimulation studies, for this task already shown to be related to activation at Wernicke's area (probe 5), a low childhood reading level would be accompanied by evidence of a shift of activation to the nearby temporoparietal region (probe 6). Since childhood abilities were the basis for reading class assignment, childhood verbal and performance IQ scores were statistically controlled when relating task-induced cortical activation to early reading ability.

In the test for the possible shift toward a more posterior focus of activation, a negative linear relationship was found between childhood reading level and flow at probe site 6 (F[2,75]=3.84, $P<.03$ in the general linear model), the temporoparietal probe site immediately posterior to Wernicke's area. Paired comparisons showed the significant differences to be between good and poor readers ($P<.01$) as well as between borderline and poor readers ($P<.01$). In addition, age, gender, state anxiety, and task order did not account for the relationship. That is, while performing this spelling task, good childhood readers were more likely to reduce (or not to activate) flow at the temporoparietal region, while poor childhood readers were more likely to increase (or not to reduce) activation at that region. A positive relationship between blood flow at Wernicke's area (probe 5) and childhood reading was found to be significant only for the comparison between good and poor readers (F[1,75]=4.30, $P<.05$; Table 3).

Of special importance for the issue of displaced function is the fact that the above inverse relationship between childhood reading and temporoparietal activity is independent of task performance: even when accuracy of task performance is entered into the general linear model, the relationship holds strong (F[2,74]=4.60, $P<.02$). By contrast, the difference in flow at Wernicke's area between extreme childhood reading levels is completely eliminated when differences due to task performance are considered, indicating the tight cou-

Table 3.—Task Performance and Childhood Reading Level Predictions of Blood Flow at Two Left Hemisphere Probe Sites for 83 Orton Subjects*

Predictor Variable	Wernicke's Area (Probe 5) F	Wernicke's Area (Probe 5) *P*	Temporoparietal Area (Probe 6) F	Temporoparietal Area (Probe 6) *P*
Task accuracy (*df* = 1,77)	7.22	<.01	0.87	>.35
Childhood reading (*df* = 2,75)	2.21	>.11	3.84	<.03
RD vs BL	1.90	>.17	5.50	<.03
RD vs NRD	4.30	<.05	6.14	<.02
BL vs NRD	1.23	>.27	0.50	>.48
Adult outcome (*df* = 2,48)	2.59	>.08	2.90	>.06
PRD vs IRD	1.01	>.31	0.06	>.80
PRD vs NI	5.16	<.03	4.52	<.04
IRD vs NI	1.95	>.16	5.11	<.03

*After taking into account variance due to age, gender, task order, and IQ. The IQ scores were the Wechsler Adult Intelligence Scale-Revised Full-Scale score for the adult behavioral measure (task accuracy) and the Wechsler Intelligence Scale for Children Verbal and Performance scores for childhood reading classification. Since adult IQ is used in calculating the adult reading discrepancy score on which adult reading level is based, only childhood IQ was a covariate in adult outcome paired comparisons. RD indicates reading disabled (n = 33); BL, borderline (n = 27); NRD, not reading disabled (n = 23); PRD, persisting reading disabled (n = 18); IRD, improved reading disabled (n = 15); and NI, never impaired (n = 23).

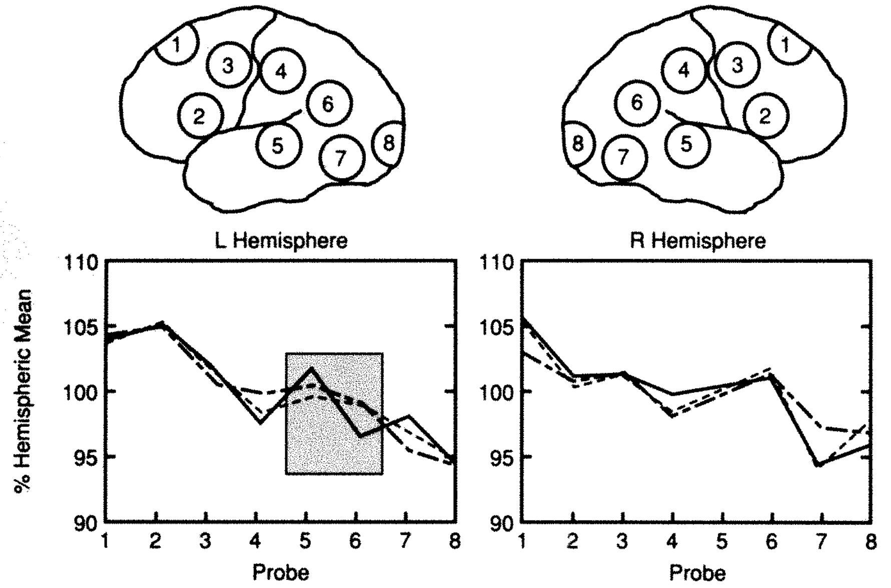

Fig 3.—Hemispheric mean corrected values plotted as a function of adult reading outcome for 56 subjects from the Orton Reading Center subject pool by adult reading outcome. Dotted line indicates persisting reading disabled (n = 18); dashed line, improved reading disabled (n = 15); and solid line, never impaired (n = 23). Probe locations are as in Fig 1.

pling between childhood reading ability and task accuracy in predicting activity specific to that site.

The high temporoparietal flow that characterized poor childhood readers was independent of the adult reading outcome of the poor childhood readers, classified according to the same two oral reading tests used to assign subjects to a childhood reading level. That is, of those who were impaired readers in childhood, the "persisting" and the "improved" subjects had the same Wernicke's area–temporoparietal rCBF profiles (Fig 3). The relationship of childhood reading level to adult blood flow in the temporoparietal region is, therefore, not simply an inverse of that found in Wernicke's area, since the temporoparietal finding is unrelated to task accuracy or to the adult reading outcome of poor childhood readers.

A visual comparison between the blood flow profile of the normal reference group (Fig 1) and the profiles of the Orton Reading Center group, plotted by reading level (Fig 2), suggests differences in the hemisphere-corrected ISIs at probes 2 and 6 in the right hemisphere. A post hoc analysis confirms that the combined Orton Reading Center group as a whole has significantly higher flow than the normal reference group at probes 2 and 6. However, the degree of activation at either probe site is unrelated to any measures of adulthood or childhood cognitive function or academic skill. It is not related to any demographic variable (eg, gender, years of education) or measured trait variable. Thus, there is no apparent relevance of these right hemisphere flow phenomena for dyslexia or other cognitive deficit. However, right temporoparietal (probe 6) flow is significantly and positively correlated with state anxiety in the combined Orton Reading Center sample. Since the anxiety scores are significantly greater in the combined Orton Reading Center sample than in the normal reference group, the best explanation for the right temporoparietal finding seems to be anxiety, not direct functional neuroanatomical differences.

COMMENT

In this investigation using the rCBF technique, a large group of normal adults showed task-specific activation of a left hemisphere region corresponding to the classic language area of Wernicke. This result from 69 normal subjects provides support for selective left superior posterotemporal mediation of this reading-related task. The finding was then confirmed in a second, more varied group of 83 adults that included some severely impaired readers. As compared with good readers, poor childhood readers activated the immediately posterior temporoparietal region more when performing this same task.

Several explanations should be considered. Cortical activation differences between dyslexic subjects and others could reflect previous verbal experience. But, in this test of the relationship between childhood reading levels and adult cortical activation, we equate the subjects for educational experience and show that the effect is still present.

Alternatively, if it can be assumed that reading-impaired subjects (who were less accurate) found the spelling task more difficult, then the greater activation of the temporoparietal region could be related to the additional effort exerted by those subjects. In fact, subject ratings of task difficulty were correlated with task performance ($r = .59$, $P < .0001$). However, the relationship between reading impairment and temporoparietal region activation does not change when subjects are equated for task performance. Therefore, effort due to task difficulty seems an insufficient explanation for the relative enhancement of the more posterior region observed in the impaired group.

The observed more posterior activity could have yet another explanation: it could reflect different strategies employed by dyslexic and normal readers. This raises the question why dyslexic subjects as a group would adopt a different strategy to do this task, a natural question for further research. A neural inefficiency hypothesis is still viable, therefore, since one logical explanation is that the use of a different strategy follows a structural insufficiency at Wernicke's area. Possibly, good readers increase Wernicke's flow and inhibit temporoparietal flow, while poor readers neither increase Wernicke's flow nor inhibit temporoparietal flow. This might suggest that good reading is served by the efficient allocation of a circumscribed left hemisphere region to verbal processing.

Alternatively, the cortical lesions presumed to develop in utero in dyslexic individuals could precipitate an atypical pattern of connectivity, in which axons normally targeted for Wernicke's region find targets within temporoparietal cortex. An example of similarly altered structural development is known from the animal literature on neural development. In studies of neonatal hamsters and ferrets, it was found that simultaneously lesioning visual target areas and auditory or somatosensory afferents resulted in stable, visually driven synaptic contacts at unoccupied auditory or somatosensory sites.[43,44] In dyslexic subjects, the more posterior termination of embryonic axons would constitute a true structural displacement, established prenatally and remaining fixed. So formed, these atypical circuits perhaps would not be as efficient as those established under nonlesion conditions and would explain why fully normal functions would not develop.

If a general displacement model is thus entertained, then the data permit a refinement of the model as follows. The full complement of functions normally represented in Wernicke's area is not entirely displaced to the more posterior locus, since a full displacement should have resulted in a correlation with task accuracy in the posterior area, contrary to the actual findings. Instead, it must be a subset of functions that is displaced (a subset whose activation at the temporoparietal site is quantitatively unrelated to task performance). On the other hand, a simple recruitment of normal temporoparietal functions (as though it were only the strategy that was shifted from Wernicke's area to the temporoparietal region) is apparently inadequate to explain the results. If that were the explanation, then poor childhood readers who improved should have shown a different temporoparietal activation from that shown by those who did not improve.

The fact of compensation must also be acknowledged as the other side of the theoretical coin. Approximately half of the Orton Reading Center group who were impaired as children read normally on the WRAT-R and Gray oral reading tests when evaluated as adults. It is plausible that those individuals who improve do so by tapping compensatory pathways, perhaps by overpractice of traditional strategies[45] or adoption of alternate strategies. We found no correlate of this compensation distinct from childhood reading, however. Thus, compensation can occur in spite of, or even because of, an underlying neural deficit and its associated anomalous activation.

In humans, the cortical correlates of compensation have not yet been described, although it has been shown that near-normal language skills can develop despite early left hemisphere lesions including hemispherectomy.[46] However, a relevant animal model for relatively normal behavior in spite of a lesion is reported by Glass.[47] Visual evoked potentials recorded over the primary visual cortex of monocularly deprived cats are permanently altered, while those recorded from a remote region assume a normal configuration once the sutured eye is opened and the animal is forced to use the "inexperienced" eye to perform certain tasks. Using this model, it would be expected that, given suitable plasticity during a critical period of development, experience would promote neural compensation for a permanent Wernicke's area loss, without necessarily inducing "excess" compensatory function elsewhere.

This study provides the first large-sample evidence that a chronic neural deficit, persisting from childhood, can be measured in vivo in adults in the left hemisphere alone, both as deficient Wernicke's area activation and as excess temporoparietal activation. As such, it not only confirms a left hemisphere anomaly in dyslexia, but also establishes, by example of existence proof, the possibility of individual differences in cortical functional landscapes.

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References

1. Horn WF, O'Donnell JP, Vitulano LA. Long-term follow-up studies of learning disabled persons. *J Learn Disabil*. 1983;16:542-555.

2. Schonhaut S, Satz P. Prognosis for children with learning disabilities: a review of follow-up studies. In: Rutter M, ed. *Developmental Neuropsychiatry*. New York, NY: Guilford Press; 1983:542-563.

3. Pennington B. Issues in the diagnosis and phenotype analysis of dyslexia: implications for family studies. In: Smith SD, ed. *Genetics and Learning Disabilities*. San Diego, Calif: College-Hill Press Inc; 1986:69-96.

4. Felton RH, Wood FB. Cognitive deficits in reading disability and attention deficit disorder. *J Learn Disabil*. 1989;22:3-22.

5. Geschwind N, Galaburda AM. Cerebral lateralization: biological mechanisms, associations and pathology. *Arch Neurol*. 1985;43:428-459.

6. Kaufmann WE, Galaburda AM. Cerebrocortical microdysgenesis in neurologically normal subjects: a histopathologic study. *Neurology*. 1989;39:238-244.

7. Galaburda AM, Sherman GF, Rosen GD, Aboitiz F, Geschwind N. Developmental dyslexia: four consecutive cases with cortical anomalies. *Ann Neurol*. 1985;18:222-233.

8. Duane DD. Commentary on dyslexia and neurodevelopmental pathology. *J Learn Disabil*. 1989;22:219-220.

9. Dvorak K, Feit J, Jurankova Z. Experimentally induced focal microgyria and status varrucosus deformis in rats. *Acta Neuropathol*. 1978;44:121-129.

10. Hier DB, LeMay M, Rosenberg PB, Perlo VP. Developmental dyslexia: evidence for a subgroup with a reversal of cerebral asymmetry. *Arch Neurol*. 1978;35:90-92.

11. Rumsey JM, Dorwart R, Vermess M, Denckla MB, Kruesi MJP, Rapoport IL. Magnetic resonance imaging of brain anatomy in severe developmental dyslexia. *Arch Neurol*. 1986;43:1045-1046.

12. Goldman PS. Neuronal plasticity in primate telencephalon: anomalous projections induced by prenatal removal of frontal cortex. *Science*. 1978;202:768-770.

13. Goldman-Rakic PS, Rakic P. Experimentally modified convolutional patterns in non-human primates: possible relevance of connections to cerebral dominance in humans. In: Geschwind N, Galaburda AM, eds. *Biological Foundation of Cerebral Dominance*. Cambridge, Mass: Harvard University Press; 1984:179-192.

14. Ojemann GA. Brain organization for language from the perspective of electrical stimulation mapping. *Behav Brain Sci*. 1983;20:189-230.

15. Mateer CA, Polen SB, Ojemann GA. Sexual variation in cortical localization of naming as determined by stimulation mapping. *Behav Brain Sci*. 1982;2:310-311.

16. Ojemann GA, Whitaker HA. Language localization and variability. *Brain Lang*. 1978;6:239-260.

17. Rasmussen T, Milner B. The role of early left-brain injury in determining lateralizations of cerebral speech functions. *Ann N Y Acad Sci*. 1977;299:355-369.

18. Glees P, Cole J. Recovery of skilled motor

functions after small repeated lesions of motor cortex in macaque. *J Neurophysiol.* 1950;13:137-148.

19. Cole J, Glees P. Effects of small lesions in sensory cortex in trained monkeys. *J Neurophysiol.* 1954;17:1-21.

20. Wood F. Theoretical, methodological, and statistical implications of the inhalation rCBF technique for the study of brain-behavior relationships. *Brain Lang.* 1980;9:1-8.

21. Wood FB. Laterality of cerebral function: its investigation by measurement of localized brain activity. In: Hellige J, ed. *Cerebral Function and Asymmetry: Method, Theory and Application.* New York, NY: Praeger Publishers; 1983:383-410.

22. Hynd, GW, Hynd CR, Sullivan HG, Kingsbury TB. rCBF in developmental dyslexia: activation during reading in a surface and deep dyslexic. *J Read Disabil.* 1987;20:294-300.

23. Rumsey JM, Berman KF, Denckla MB, Hamberger SD, Kruesi J, Weinberger DR. Regional cerebral blood flow in severe developmental dyslexia. *Arch Neurol.* 1987;44:1144-1150.

24. Naylor CE, Felton RH, Wood FB. Adult outcome in developmental dyslexia. In: Pavlidis G, ed. *Dyslexia: A Neuropsychological and Learning Perspective.* New York, NY: John Wiley & Sons Inc; 1990:213-229.

25. Wechsler D. *Manual for the Wechsler Adult Intelligence Scale–Revised.* New York, NY: Psychological Corp; 1981.

26. Wechsler D. *Manual for the Wechsler Intelligence Scale for Children.* New York, NY: Psychological Corp; 1949.

27. Boder E, Jarrico S. *The Boder Test of Reading-Spelling Patterns: A Diagnostic Screening Test for Subtypes of Reading Disability.* New York, NY: Grune & Stratton; 1982.

28. Gray WS. *Standardized Oral Reading Paragraphs.* Indianapolis, Ind: Bobbs-Merrill Co Inc; 1955.

29. Jastak J, Bijou S. *Wide Range Achievement Test.* Wilmington, Del: Jastak Associates Inc; 1945.

30. Jastak S, Wilkinson G. *Wide Range Achievement Test–Revised Administration Manual.* Wilmington, Del: Jastak Associates Inc; 1984.

31. Finucci JM, Whitehouse CC, Isaacs SD, Childs B. Derivation of validation of a quantitative definition of specific reading disability for adults. *Dev Med Child Neurol.* 1984;26:143-153.

32. Briggs GG, Nebes RD. Patterns of hand preference in a student population. *Cortex.* 1975;11:230-238.

33. Stump DA, Williams R. The noninvasive measurement of regional cerebral circulation. *Brain Lang.* 1980;9:35-46.

34. Risberg J, Ali Z, Wilson EM, Willis EL, Halsey JH. rCBF by ^{133}xenon inhalation: preliminary evaluation of an ISI in patients with unstable flow compartments. *Stroke.* 1975;6:142-148.

35. Paivio A, Yuillo JC, Madigan SA. Concreteness, imagery and meaningfulness values for 925 nouns. *J Exp Psychol.* 1968;76:1-23.

36. Naritomi H, Meyer JS, Sakai F, Yamaguchi F, Shaw T. Effects of advancing age on rCBF. *Arch Neurol.* 1979;36:410-416.

37. Hannay HJ, Leli DA, Falgout JC, et al. rCBF for middle-aged males and females during right-left discrimination. *Cortex.* 1983;19:465-474.

38. Risberg J, Maxmilian A, Prohovnik I. Changes of cortical activity patterns during habituation to a reasoning test. *Neuropsychologia.* 1977;15:793-798.

39. Wood FB, Armentrout R, Toole JF, McHenry L, Stump D. rCBF response during rest and memory activation in a patient with global amnesia. *Brain Lang.* 1980;9:129-136.

40. Green DM, Swets J. *Signal Detection Theory.* New York, NY: John Wiley & Sons Inc; 1966.

41. Ingvar DH. Hyperfrontal distribution of the cerebral grey matter flow in resting wakefulness on the functional anatomy of conscious states. *Acta Neurol Scand.* 1979;60:12-25.

42. Spielberger CD, Gorsuch RL, Luchene R, Vagg PR, Jacobs GA. *Manual for the State-Trait Anxiety Inventory (STAI): Form Y.* Palo Alto, Calif: Consulting Psychology Press; 1983.

43. Sur M, Garraghty PE, Roe AW. Experimentally induced visual projections into auditory thalamus and cortex. *Science.* 1988;242:1437-1440.

44. Frost DD. Mechanisms of structural and functional development in the thalamus: retinal projections to the auditory and somatosensory systems in normal and experimentally manipulated hamsters. In: Bentivoglio M, Spreafico R, eds. *Cellular Thalamic Mechanisms.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1988:447-464.

45. Bradley L, Bryant P. Categorizing sounds and learning to read: a causal connection. *Nature.* 1983;302:419-421.

46. Dennis M, Whitaker HA. Language acquisition following hemi-decortication: linguistic superiority of the left over the right hemisphere. *Brain Lang.* 1976;3:404-433.

47. Glass JD. Photically evoked potentials from cat neocortex before and after recovery from visual deprivation. *Exp Neurol.* 1973;39:123-139.

Validation of a Clinical Antisaccadic Eye Movement Test in the Assessment of Dementia

Jon Currie, FRACP; Ben Ramsden; Cheryl McArthur; Paul Maruff

• The ability to generate antisaccades (eye movements deliberately made in the direction opposite to that of a visual stimulus) may be used to assess central nervous system function in a variety of neurologic and psychiatric disorders. However, the usefulness of this paradigm in clinical practice is limited by the need for an oculographic laboratory. We describe a clinical version of such an antisaccadic task and present normative data from 332 subjects. We also examined clinical antisaccades and cognitive performance in 30 patients with Alzheimer's disease, five patients with Huntington's disease, and 12 patients with pseudodementia. In Alzheimer's disease, error rates in the clinical antisaccadic test correlated well with those from a laboratory-based antisaccadic task measured on the same day by infrared oculography, confirming that the clinical antisaccadic test is a valid analog of the more sophisticated laboratory paradigms. Clinical antisaccadic error rates correlated strongly with the severity of dementia in Alzheimer's disease, and correlations with cognitive performance suggested that the clinical antisaccadic test may have some specificity for frontal lobe dysfunction. Patients with pseudodementia had normal clinical antisaccadic error rates, and the test may therefore be of use in differentiating dementia from pseudodementia. This clinical antisaccadic test provides a simple, reliable, and inexpensive quantitative clinical tool that is of value in the assessment of disturbances of higher cortical function.

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Laboratory measurement of eye movements has assumed increasing importance in the assessment of abnormalities of central nervous system function in a variety of neurologic and psychiatric disorders that include Alzheimer's disease,[1-4] Huntington's disease,[5,6] progressive supranuclear palsy,[7] Parkinson's disease,[8] schizophrenia,[9,10] and the acquired immunodeficiency syndrome.[11,12] Of particular value is the analysis of voluntary eye movements that result from more complex visual cognitive or memory tasks, such as the ability to generate antisaccades.[3,5,7,9,10,12] *Antisaccades* are eye movements deliberately made in the direction opposite to that of a suddenly presented peripheral stimulus and require the suppression of any reflexive eye movement toward that stimulus.[13-15] The ability to suppress a reflexive glance at a target, but to use the target's visual information accurately to move the eyes in the opposite direction, is thought to utilize corticotectal pathways that originate from several areas of the frontal cortex and descend via the caudate nucleus, substantia nigra, and superior colliculus.[7,10,15-18] Abnormalities of both antisaccadic accuracy and latency occur with cortical and subcortical lesions that involve these areas.[5-7,15]

Two major drawbacks to the routine use of high-resolution eye movement measurement in clinical neurologic practice are the need for a laboratory setting and the cost of the equipment required. Although laboratory recording techniques significantly increase the ability to detect and quantify different eye movement abnormalities,[19] clinical examination of eye movements can still play a valuable role in the examination of many neurologic diseases.[20] This report describes and validates a clinical antisaccadic eye movement test and illustrates its use in the clinical assessment of dementia in patients with Alzheimer's disease.

SUBJECTS AND METHODS

Clinical Protocol for the Antisaccadic Eye Movement Test

The subject was seated facing the examiner, who positioned his hands equidistantly from the midline in the subject's left and right visual fields, with each index finger extended in the manner commonly used to test visual fields by confrontation. The stimulus for each trial was two to five rapid, repeated flexions of one or the other of the examiner's index fingers. A saccadic and antisaccadic task were performed, the saccadic task acting as a training session for the antisaccadic test.

Saccadic Task.—The subject was instructed to remain looking at the examiner's nose until one of the examiner's index fingers moved and then as quickly as possible to "turn your eyes only and look at the finger that moves." Following either a correct or incorrect response, the subject was then instructed to look back at the examiner's nose, and each subsequent trial was not begun until this central fixation was clearly reestablished. The task was therefore paced by the subject's responses. A random sequence of six to 10 saccades to the subject's right and left, looking at the moving finger, was then performed. This allowed the subjects to learn not to anticipate a predictable sequence of steps from one side to the other, and to learn to move only their eyes to look at the target and not to point with the hand or verbally indicate left or right, as is commonly done with visual field testing. The subject's response was recorded as the direction of the initial movement of the eyes from the midline in response to the movement of the examiner's finger. A correct response for the saccadic task was an initial eye movement toward the moving finger. The saccades were continued until the subject could perform the task correctly.

Antisaccadic Task.—The subject was then informed that the task had changed and given the following instruction by the examiner: "When my finger moves, do not look at the finger that moves, look immediately in the opposite direction at the finger that does not move." For the antisaccadic task, the correct response was an initial eye movement to the side opposite that of the moving finger, and any initial eye movement across the midline toward the moving finger was recorded as an error, even if a subsequent correction toward the nonmoving finger was made. If comprehension of the task seemed incomplete, the subject was asked to point with a finger at the correct, opposite, nonmoving target, to demonstrate that the principles of the test were understood. Once the concept of the task had been established, 25

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trials were performed with random determination of laterality, and again central fixation was reestablished after each trial before continuing to the next trial. The first five of these 25 trials were regarded as practice trials and were not scored, and the instructions could be repeated during these five trials to ensure that the task was understood. The examiner then scored the number of correct responses for the subsequent 20 trials. Brief positive verbal reinforcement was given after each trial, and the instructions for the task were repeated if two successive incorrect responses occurred. A percentage error rate was calculated for the antisaccadic task as follows: (Number of antisaccadic errors/total number of trials) × 100.

In 15 control subjects (eight male, seven female; mean age, 43 years; age range, 15 to 80 years), the eye movement responses elicited during this clinical antisaccadic testing were recorded using infrared scleral reflectance oculography (IRIS, Skalar, Delft, the Netherlands) and a computer timing switch initiated by the flexion movement of the examiner's finger (Fig 1). In these 15 control subjects and in 15 subjects with Alzheimer's disease, the error rate in the clinical antisaccadic testing was also correlated with the error rate recorded on the same day by infrared oculography during a typical laboratory-based antisaccadic task, similar to that described by Lasker et al.[5] In this laboratory-based task, subjects fixated a central green light-emitting diode target, which was then extinguished simultaneously with the appearance of a peripheral red target positioned either to the left or right of midline. The red target was laser generated and computer controlled using X-Y mirror galvanometers (General Scanning, Watertown, Mass). Displacement and timing of the appearance of the peripheral red target was pseudorandom, with 7.5°, 10°, or 15° steps and 2.0- or 2.5-second intervals after fixation. The subject was instructed not to look at the red target but immediately to look at an imagined point an equal distance on the opposite side of the midline and to hold the gaze there until returning to central fixation with the reappearance of the central green target.

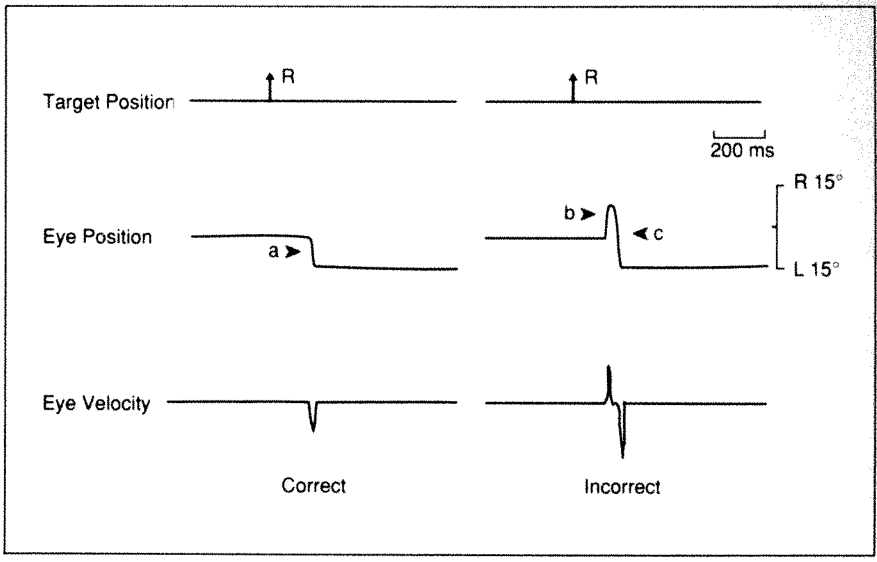


Fig 1.—Infrared eye movement recordings during the clinical antisaccadic task for a "moving finger" target to the right (R) of the subject's midline showing a correct leftward eye movement in the direction opposite to that of the moving finger (a) and an incorrect rightward initial eye movement toward the moving finger (b) with a subsequent corrective eye movement to the opposite side (c). Note also that the latency of response for the correct antisaccade is longer than for the reflexive, incorrect antisaccade.

Subjects

Control Subjects.—There were 332 control subjects, including 180 healthy volunteers (83 male, 97 female; age range, 15 to 89 years, with a mean age [±SD] of 41±18 years) and 152 hospital inpatients and outpatients with a variety of nonneurologic illnesses (65 male, 87 female; age range, 15 to 87 years, with a mean age of 52±21 years).

Patient Groups.—There were three patient groups. First was a group of 30 patients with clinically diagnosed Alzheimer's disease (16 male, 14 female; age range, 49 to 89 years, with a mean age of 67±8 years). Their disease was diagnosed according to National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association criteria,[21] including gradual deterioration of memory and intellectual function over a period of at least 2 years, an ischemic score[22] below 4, and computed tomographic or magnetic resonance imaging scanning to exclude coexisting focal structural disease. All patients had severity of dementia assessed by the Mini-Mental State examination (MMSE).[23] Where possible (n=20), a neuropsychometric test battery was administered, which included the modified Weigl Color Form Sorting (CFS) test,[24] the Digit Span Forward subtest of the Wechsler Adult Intelligence Scale,[25] the Memory Quotient of the Wechsler Memory Scale,[26] and the Buschke Selective Reminder Test.[27]

Second was a group of 10 patients with depressive pseudodementia (*Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition* [*DSM-III-R*] criteria[28(pp106,221)]) (six male, four female; age range, 35 to 84 years) and two with factitious disorder with psychological symptoms (*DSM-III-R* criteria[28(pp318-319)]) (both female).

Third was a group of five patients with Huntington's disease (four male, one female; age range, 18 to 64 years).

The research protocol was approved by the Ethics Committee of the Mental Health Research Institute of Victoria, Parkville, Australia. Subjects or their next of kin gave informed consent after the nature of the testing had been fully explained.

Statistical Analysis

In general, comparisons between groups were performed by analysis of variance with post hoc comparisons by Scheffé's test. Correlations were performed by the Pearson Product-Moment Correlation Coefficient or Spearman Rank-Order Correlation, as indicated. Significance was taken at $P \leq .01$ unless otherwise stated.

RESULTS

Control Subjects

In the 15 control subjects where the clinical antisaccadic task was recorded with infrared oculography, the mean latency for a correct antisaccade was 324±96 milliseconds, and for an incorrect, reflexive saccade toward the target the mean latency was 282±159 milliseconds (Fig 1). By comparison, for the laboratory-based task with the same subjects, the latency for a correct antisaccade was 336±93 milliseconds and for an incorrect reflexive saccade it was 285±109 milliseconds. Infrared oculography also demonstrated that an examiner could accurately identify all correct and incorrect saccades performed during the clinical task.

For the clinical antisaccadic task, the percent error rate was independent of subject age above 15 years ($r = .122$, $P < .02$), and there was no statistical difference between the error rates of male and female subjects in either the healthy volunteer group or the hospital inpatient and outpatient group. The results for male and female subjects were therefore combined across all ages within each of these two control subject groups (Fig 2). The mean percent error rate in the hospital control group (10.3%±6.3%) was slightly higher than in the healthy volunteer group (8.3%±6.7%), but this difference did not reach significance ($P = .08$). Results from both groups were combined together (mean, 9.2%±6.6%), and a 99th percentile error score control range was defined for the antisaccadic task (Fig 3). Scores of 30% or greater were considered abnormal. By comparison, for the laboratory-based task, the mean percent error rate was 6.2%±7.8%. From the total control population, a subgroup (n = 152; age range, 49 to 87 years with a mean age of 65 ± 10 years) was also selected that was age matched with the group with Alzheimer's disease. For this control subgroup, the mean percent error rate was 10.1% ± 6.3%, and scores of 30% or greater were also abnormal at the 99th percentile.

Clinical Patient Groups

Twenty-five (83%) of the 30 patients with Alzheimer's disease had impaired performance (≥30% error rate) in the clinical antisaccadic task, and the percent error rate correlated strongly with the severity of dementia present, as measured by the MMSE score ($r = -.935$, $P < .0001$; Fig 4, left). All 26 patients with MMSE scores less than 25 (abnormal performance defined by age-specific norms[29]) had antisaccadic error rates of 30% or greater. There was also a strong correlation between the clinical antisaccadic error rate and the error rate in performing the laboratory antisaccadic task as measured by infrared oculography ($r = .921$, $P < .0001$; Fig 5). In almost all cases, the percent error rates from the laboratory-based task were higher than those with the clinical antisaccadic test. The clinical antisaccadic percent error rate correlated strongly with patients' scores on the CFS test ($r = -.917$, $P < .0001$; Fig 4, right) and had intermediate correlations with tests of memory function (Memory Quotient, $r = -.807$, $P < .001$; Selective Reminder Test, $r = -.716$, $P = .004$) but poor correlation with scores on the Wechsler Adult Intelligence Scale Digit Span Forward subtest ($r = -.489$, $P > .05$).

In contrast to patients with Alzheimer's disease, the antisaccadic error rates in patients with depressive pseudodementia or factitious disorder were normal once compliance for testing was gained, despite significantly impaired global levels of cognitive performance (Fig 6).

All five patients with Huntington's disease had increased antisaccadic error rates that were slightly higher than

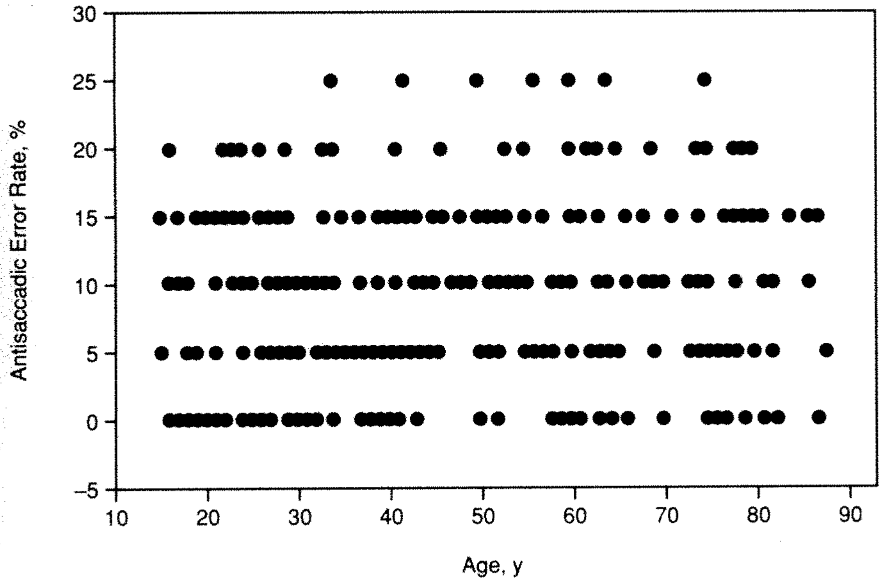


Fig 2.—Clinical antisaccadic percent error rate for all control subjects over the age of 15 years (n = 332), showing no correlation of percent error rate with subject age.

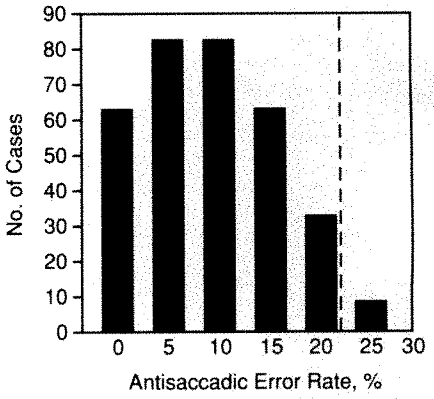
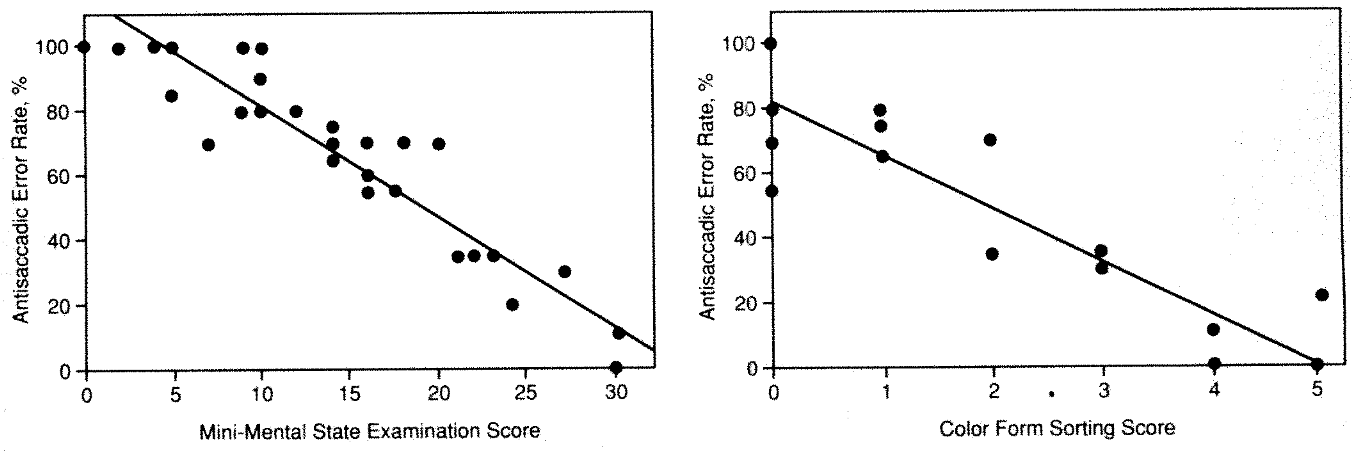


Fig 3.—Frequency histogram showing the distribution of percent error rates for the clinical antisaccadic test in the control population. The error rate control range was 0% to 25%, and an error rate above 25% was considered to be abnormal. The vertical broken line indicates mean + 2 SDs.

Fig 4.—Correlation in 30 patients with Alzheimer's disease between the clinical antisaccadic percent error rates and Mini-Mental State examination scores (left) ($r = -.935$, $P < .0001$) and Color Form Sorting scores (right) ($r = -.917$, $P < .0001$).



those for patients with Alzheimer's disease with similar MMSE scores (Fig 6).

COMMENT

The clinical antisaccadic test is simple to administer and provides a measure of oculomotor function in patients with Alzheimer's disease that correlates well with the severity of dementia.

Correct performance of an antisaccadic task requires a subject to suppress the reflexive, prepotent tendency to look at a newly presented visual stimulus, but to use the target's visual information to move the eyes immediately in the opposite direction.[5-7,13-17] This requires the generation of both excitatory and inhibitory oculomotor signals, as well as utilizing representational memory of what the target means, rather than using the direct stimulation that is immediately present in the target.[17] In monkeys, the control of such voluntary, purposive saccades is probably dependent on the interaction of a variety of regions in the frontal cortex,[17] including the areas of the frontal eye fields (FEFs)[18,30] and principal sulcus[31] in the dorsolateral prefrontal cortex, and the supplementary eye field region in the dorsomedial frontal cortex.[32] The prefrontal cortex may issue both facilitatory and inhibitory motor commands that could accomplish the dual task of commanding the correct response while disallowing or inhibiting the incorrect one.[17,18] For example, the FEF provides both direct targeting signals to the superior colliculus, as well as foveally responsive signals, which may trigger or suppress collicular saccades.[18] In addition, the FEF may influence the substantia nigra, via an FEF–caudate nucleus pathway.[16,18,33] The FEF projects to the head of the caudate, which contains a presaccadic signal similar in quantity but reversed in sign from that of the substantia nigra. This frontal-caudate signal may inhibit the substantia nigra and result in release of the tonic nigral suppression of the superior colliculus.[18,33] Similarly, the supplementary eye field of the dorsomedial frontal cortex provides longer-latency saccadic signals to the superior colliculus related to goal-directed and self-initiated saccades.[32] These pathways from the frontal cortex and basal ganglia to the superior colliculus control the generation of volitional, visually guided eye movements[7,15,18,30] and may help to suppress reflexive glances toward visual stimuli by inhibiting the superior colliculus.[7,15,18]

Impaired antisaccadic performance is usually attributed to lesions that involve these pathways.[5,7,15,17] A prominent feature in subjects with frontal lobe lesions is distractibility due to excessive dependence on, or sensitivity to, external cues.[17,34,35] In the antisaccadic task, this is demonstrated by an inability to suppress forbidden, reflexive eye movements toward each newly presented target. In addition, subjects with frontal lobe lesions have difficulty using the representational information from the initial target to move the eye correctly in the opposite direction,[17] and often the correct eye movement is only triggered if a second cue is subsequently provided to indicate the correct, expected eye position.[15]

As in the laboratory-based antisaccadic paradigm, the clinical antisaccadic task described herein also provides an initial target (moving finger) with which to assess the ability to suppress incorrect reflexive saccades (distractibility). The clinical task does differ slightly from the laboratory task in that the secondary cue for the correct location for the antisaccadic eye movement (the opposite, nonmoving finger) is continually present. However, for our 15 control subjects, performance in both the clinical and laboratory tests was similar. Our results using the clinical antisaccadic test are also in close agreement with previously reported results from laboratory antisaccadic paradigms.[3,5,7,9,10,15] For control subjects, the clinical test error rates (0% to 25%) and latencies for both correct (324 milliseconds) and incorrect (282 milliseconds) antisaccadic responses accord well with those reported previously for laboratory control subjects (error rates, 5% to 20%[9,15]; correct antisaccadic latencies, 250 to 364 milliseconds[5,9]; latencies for incorrect saccades, 219 to 311 milliseconds[5,10]). As with laboratory paradigms, the latency for correct clinical antisaccades was longer than for incorrect (reflexive) initial eye movements[15] (Fig 1).

Patients with Alzheimer's disease performing the clinical antisaccadic test showed difficulty both in suppressing incorrect responses and in generating correct responses in the opposite direction. In these patients, the strong correlation of clinical error rates with laboratory error rates (Fig 5) also supports the validity of the clinical paradigm. How-

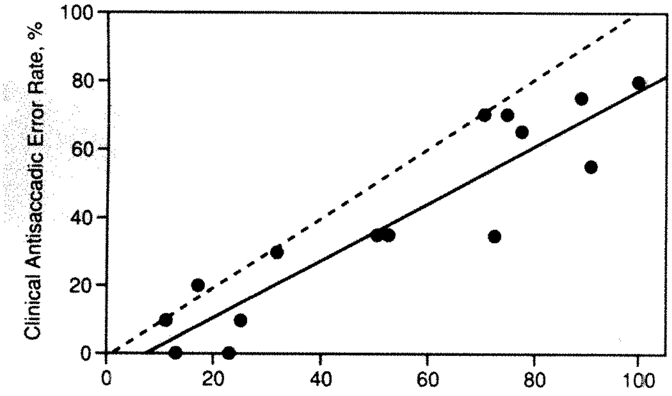


Fig 5.—Correlation in 15 patients with Alzheimer's disease between the percent error rates in the clinical antisaccadic task and percent error rates in a laboratory-based antisaccadic task performed on the same day. The dotted line represents the ideal regression if the error rates in the two tasks were equal, and the solid line is the linear regression for the actual error values obtained. The laboratory-based task has higher percent error rates than the clinical test in almost all cases (values lying below the dotted line) and is therefore likely to be a more sensitive test (r=.921, P<.0001).

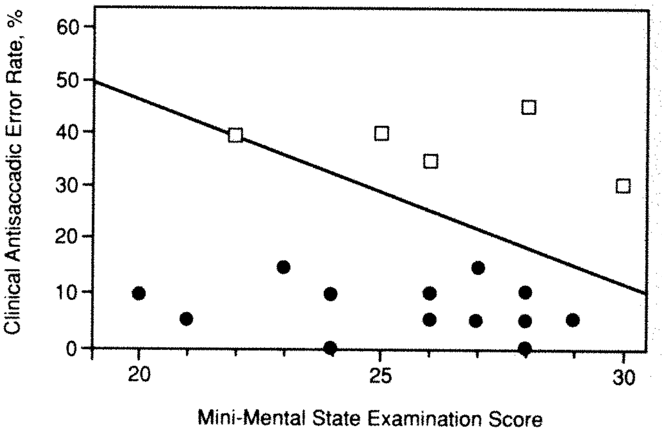


Fig 6.—Correlation of clinical antisaccadic percent error rates and Mini-Mental State examination scores in 12 patients with depressive pseudodementia (solid circles) and five patients with Huntington's disease (open squares), illustrated in relation to the linear regression line for percent error rates in patients with Alzheimer's disease from Fig 4, left. In general, error rates in patients with Huntington's disease are higher and in patients with pseudodementia are lower than in patients with Alzheimer's disease.

ever, the higher laboratory error rates in patients with Alzheimer's disease suggest that laboratory techniques are still more sensitive than clinical examination.[19] In Alzheimer's disease, the error rates for the clinical antisaccadic test correlated strongly with the severity of dementia present (Fig 4, left). Fletcher and Sharpe[3] have previously reported decreased ability to make antisaccades in patients with Alzheimer's disease but did not comment on any correlation of error rate with disease severity. Our findings suggest that the clinical antisaccadic test may be useful in the clinical assessment of dementia in Alzheimer's disease and in monitoring disease progression. The striking difference in error rates between patients with Alzheimer's disease and those with depressive pseudodementia functioning at comparable levels, as measured by MMSE scores (Fig 6), suggests that the test may also be useful in distinguishing between these two conditions.

Guitton et al[15] have demonstrated that frontal lobe lesions give rise to difficulties in generating antisaccades. In Alzheimer's disease, Fletcher and Sharpe[3] have also attributed antisaccadic abnormalities to neuronal degeneration in the frontal cortex. The CFS is a test that particularly relies on frontal lobe function.[36(pp484-486)] In our patients with Alzheimer's disease, there was a strong correlation of antisaccadic error rates with performance in the CFS test (Fig 4, right), but not with Digit Span Forward. Digit Span Forward is primarily a measure of the efficiency of attention and is relatively resistant to the effects of dementia but may be influenced by factors such as anxiety.[36(pp266-270)] These findings support the conclusion that frontal lobe damage may be contributing to impaired antisaccadic performance in patients with Alzheimer's disease.

Saccadic distractibility and poor antisaccadic performance have also been reported in patients with Huntington's disease[5] and progressive supranuclear palsy,[7] which may reflect abnormalities of basal ganglia function rather than frontal lobe function. In our patients with Huntington's disease, the antisaccadic error rates were higher than those in patients with Alzheimer's disease with comparable MMSE scores (Fig 6). Lasker et al[5] reported a similarly high antisaccadic error rate (mean, 60%) in patients with mild Huntington's disease, and no patients made fewer than 20% errors. These findings may reflect the important role that the basal ganglia and other subcortical structures play in the initiation of voluntary saccades and maintenance of fixation.

The antisaccadic test that we have described appears to be a valid clinical analog of the more sophisticated laboratory-based antisaccadic paradigms. Error rates in this clinical test correlate well with the severity of dementia in Alzheimer's disease and may have some specificity for frontal lobe dysfunction. Although the abnormalities that are detected with this clinical antisaccadic test are not necessarily specific for any single disease, we believe that the test provides a simple, robust, and inexpensive quantitative clinical tool that will be of value in the assessment of disturbances of higher cortical function.

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References

1. Pirozzolo FJ, Hansch EC. Oculomotor reaction time in dementia reflects degree of cerebral dysfunction. *Science*. 1981;214:349-351.
2. Hershey LA, Whicker L, Abel LA, Dell'Ossa LF, Traccis S, Grossniklous D. Saccadic latency measurements in dementia. *Arch Neurol*. 1983;40:592-593.
3. Fletcher WA, Sharpe JA. Saccadic eye movement dysfunction in Alzheimer's disease. *Ann Neurol*. 1986;20:464-471.
4. Fletcher WA, Sharpe JA. Smooth pursuit dysfunction in Alzheimer's disease. *Neurology*. 1988;38:272-277.
5. Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS. Saccades in Huntington's disease: initiation defects and distractibility. *Neurology*. 1987;37:364-370.
6. Lasker AG, Zee DS, Hain TC, Folstein SE, Singer HS. Saccades in Huntington's disease: slowing and dysmetria. *Neurology*. 1988;38:427-431.
7. Pierrot-Deseilligny CH, Rivaud S, Pillon B, Fournier E, Agid Y. Lateral visually-guided saccades in progressive supranuclear palsy. *Brain*. 1989;112:471-487.
8. Rascol O, Clanet M, Montastruc JL, et al. Abnormal ocular movement in Parkinson's disease: evidence for involvement of dopaminergic systems. *Brain*. 1989;112:1193-1214.
9. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol Psychiatry*. 1988;23:670-677.
10. Thaker GK, Nguyen JA, Tamminga CA. Increased saccadic distractibility in tardive dyskinesia: functional evidence for subcortical GABA dysfunction. *Biol Psychiatry*. 1989;25:49-59.
11. Currie J, Benson E, Ramsden B, Perdices M, Cooper D. Eye movement abnormalities as a predictor of the acquired immunodeficiency syndrome dementia complex. *Arch Neurol*. 1988;45:949-953.
12. Currie J, Ramsden B, McArthur C, et al. High resolution eye movement recording in the assessment of neurologic involvement in HIV-1 infection. *EEG EMG*. 1989;20:273-279.
13. Hallett PE. Primary and secondary saccades to goals defined by instructions. *Vision Res*. 1978;18:1279-1296.
14. Hallett PE, Adams BD. The predictability of saccadic latency in a novel voluntary oculomotor task. *Vision Res*. 1980;20:329-339.
15. Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res*. 1985;58:455-472.
16. Wurtz RH, Hikosaka O. Role of the basal ganglia in the initiation of saccadic eye movements. *Prog Brain Res*. 1986;64:175-189.
17. Goldman-Rakic P. Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In: Plum F, Mountcastle V, eds. *Handbook of Physiology*. Bethesda, Md: American Physiology Society; 1987;5:373-417.
18. Segraves M, Goldberg M. Functional properties of corticotectal neurons in the monkey's frontal eye field. *J Neurophysiol*. 1987;56:1387-1419.
19. Meienberg O, Muri R, Rabineau PA. Clinical and oculographic examination of saccadic eye movements in the diagnosis of multiple sclerosis. *Arch Neurol*. 1986;43:438-443.
20. Leigh R, Zee D. *The Neurology of Eye Movements*. Philadelphia, Pa: FA Davis Co Publishers; 1983.
21. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 1984;34:939-944.
22. Hachinski VC, Hiff LD, Zalkha E, et al. Cerebral blood flow in dementia. *Arch Neurol*. 1975;32:632-637.
23. Folstein M, Folstein S, McHugh PR. Mini-Mental State: a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res*. 1975;12:189-198.
24. De Renzi E, Spinnler H. Visual recognition in patients with unilateral cerebral disease. *J Nerv Ment Dis*. 1966;142:515-525.
25. Wechsler D. *The Wechsler Adult Intelligence Scale–Revised*. New York, NY: The Psychological Corp; 1981.
26. Wechsler D. A standardized memory scale for clinical use. *J Psychol*. 1945;19:87-95.
27. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology*. 1974;11:1019-1025.
28. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition*. Washington, DC: American Psychiatric Association; 1987:106, 221, 318-319.
29. Bleecker M, Bolla-Wilson K, Kawas C, Agnew J. Age-specific norms for the Mini-Mental State Exam. *Neurology*. 1988;38:1565-1568.
30. Deng SY, Goldberg ME, Segraves MA, Ungerleider LG, Mishkin M.The effect of unilateral ablation of the frontal eye fields on saccadic performance in the monkey. In: Keller EL, Zee DS, eds. *Adaptive Processes in Visual Oculomotor Systems*. Elmsford, NY: Pergamon Press Inc; 1986:201-208.
31. Boch R, Goldberg M. Participation of prefrontal neurons in the preparation of visually guided eye movements in the rhesus monkey. *J Neurophysiol*. 1989;61:1064-1083.
32. Schlag J, Schlag-Rey M. Evidence for a supplementary eye field. *J Neurophysiol*. 1987;57:179-200.
33. Hikosaka O, Sakamoto M, Usui S. Functional properties of monkey caudate neurons, I: activities related to saccadic eye movements. *J Neurophysiol*. 1989;61:780-798.
34. Lhermitte F, Pillon B, Serdaru M. Human autonomy and the frontal lobes, I: imitation and utilization behaviour: a neuropsychological study of 75 patients. *Ann Neurol*. 1986;19:326-334.
35. Lhermitte F. Human autonomy and the frontal lobes, II: patient behaviour in complex social situations: the 'environmental dependency syndrome.' *Ann Neurol*. 1986;19:335-343.
36. Lezak MD. *Neuropsychological Assessment*. 2nd ed. New York, NY: Oxford University Press Inc; 1983.

Literary Neurologic Syndromes

Alice in Wonderland

Loren A. Rolak, MD

• **Many neurologic syndromes are named for literary characters. For example, the "Alice in Wonderland" syndrome of altered body perceptions, usually caused by migrainous ischemia, is so called because of the resemblance of its symptoms to the fluctuations in size and shape that plague the main character in Lewis Carroll's 1865 novel *Alice in Wonderland*. The medical symptoms of distorted body images match the literary description so precisely that illustrations from the original book depict them very accurately. Because Lewis Carroll suffered from classic migraine headaches, scholars have speculated that he may have experienced this syndrome himself.**

(*Arch Neurol*. 1991;48:649-651)

The "Alice in Wonderland" syndrome refers to distortions of body image, usually in the setting of classic migraine headaches. Todd[1] gave the syndrome its literary name in his report in the November 1, 1955, issue of the *Canadian Medical Association Journal*, describing "a singular group of symptoms intimately associated with migraine and epilepsy." However, the first description of the condition was by Lippman[2] in the *Journal of Nervous and Mental Diseases* in 1952.

In his report, titled "Certain Hallucinations Peculiar to Migraine," Lippman[2] described seven patients with migraine headaches who described altered perceptions of their body image. Often, these appeared as migraine equivalents, in which the hallucinations constituted the entire attack; there was no accompanying headache, scotoma, nausea, or any other physical symptom to lend credence to these bizarre distortions. Lippman used direct quotations from his patients to emphasize the peculiar alterations of bodily perception that constitute this syndrome. His patient 2 had the sensation of her left ear "ballooning out 6 inches or more." His patient 3 described the following:

> I felt that I was very tall. When walking down the street, I would think I would be able to look down on the tops of others' heads, and it was very frightening and annoying not to see as I was feeling. The sensation was so real that when I would see myself in a window or full-length mirror, it was quite a shock to realize that I was still my normal height of under 5 feet.

Lippman's patient 7 described his sensations as follows: "The body is as if someone had drawn a vertical line separating two halves. The right half seems to be twice the size of the left half." Victims were aware of the illusory nature of their perceptions but were sometimes reluctant to admit to them for fear of being thought insane.

Some of these patients also had distortions of time sense, such as "I felt as if I was going fast," and "I felt as if everyone was talking too fast and moving too fast." The patients' ages ranged from 11 to 72 years, although the syndrome, like migraine, appears to be more common in young people, even children. Although a variety of causes, including viral encephalitis[3] and epilepsy,[2] subsequently have been reported for the Alice in Wonderland syndrome, it is almost pathognomonic of migraine.[4]

This sensation of formed body distortions, a type of metamorphopsia, probably results from migrainous ischemia. Different authors analyzing this syndrome have come to different conclusions about its localization, some asserting that the pathology affects the anterior occipital lobe, while others implicate the posterior temporal lobe. Most, however, believe that the symptoms arise in the posterior parietal lobe, especially from the nondominant hemisphere.[2-4]

The name of the syndrome comes from the book most people know as *Alice in Wonderland*,[5] although its actual title is *Alice's Adventures in Wonderland*, often printed with its companion piece *Through the Looking-Glass and What Alice Found There*. The story was published in 1865 by Charles Lutwidge Dodgson, under the pseudonym Lewis Carroll. Dodgson was an English gentleman who attended Rugby and Oxford University, where he became a professor of mathematics, specializing in Euclidean geometry. He was considered a first-class mathematician, and, indeed, his fictional works, such as *Alice in Wonderland*, have been analyzed from the standpoint of mathematical theory.[6] In fact, the action in the book corresponds to a real and complex chess game, with the adventures and movements of Alice, the Red Queen, the White Knight, and other characters representing actual moves on a chessboard (Fig 1).

An episode of changing height is one of the most famous scenes in the book. At one point, Alice finds a bottle marked

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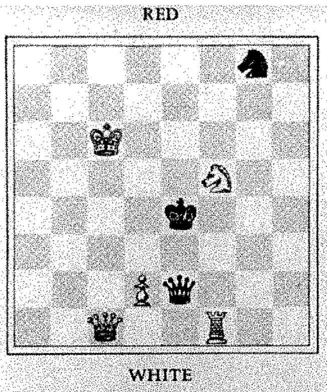

1. Alice meets R. Q.	1. R. Q. to K. R's 4th
2. Alice through Q's 3d *(by railway)* to Q's 4th *(Tweedledum and Tweedledee)*	2. W. Q. to Q. B's 4th *(after shawl)*
3. Alice meets W. Q. *(with shawl)*	3. W. Q. to Q. B's 5th *(becomes sheep)*
4. Alice to Q's 5th *(shop, river, shop)*	4. W. Q. to K. B's 8th *(leaves egg on shelf)*
5. Alice to Q's 6th *(Humpty Dumpty)*	5. W. Q. to Q. B's 8th *(flying from R. Kt.)*
6. Alice to Q's 7th *(forest)*	6. R. Kt. to K's 2nd (ch.)
7. W. Kt. takes R. Kt.	7. W. Kt. to K. B's 5th
8. Alice to Q's 8th *(coronation)*	8. R. Q. to K's sq. *(examination)*
9. Alice becomes Queen	9. Queens castle
10. Alice castles *(feast)*	10. W. Q. to Q. R's 6th *(soup)*
11. Alice takes R. Q. & wins	

Fig 1.—The chess problem that is the basis for the actions and movements of the characters in *Alice in Wonderland,* as the white pawn (Alice) advances to capture the red queen (R. Q.) and win the game. Q indicates queen; W. Q., white queen; W. Kt., white knight; R. Kt., red knight; K. R., king's rook; K. B., king's bishop; Q. B., queen's bishop; and K. sq., king's square.

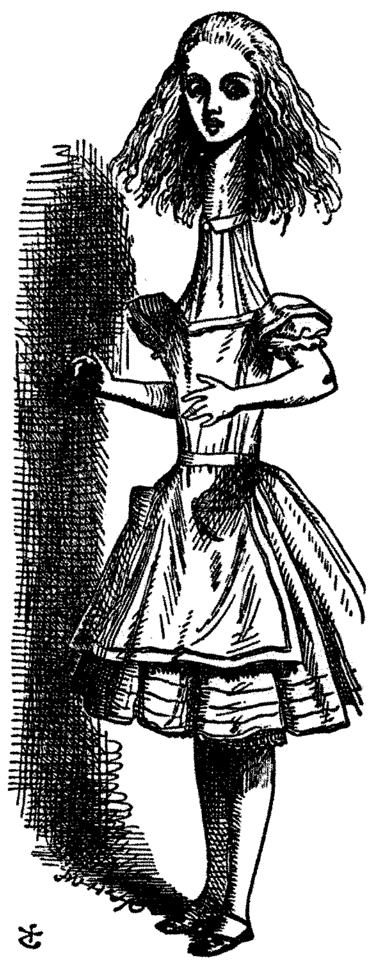

Fig 3.—Lippman's patient 6 indicated that "I get all tired out from pulling my head down from the ceiling. My head feels like a balloon; my neck stretches and my head goes to the ceiling. I've been pulling it down all night long." This description matches this original illustration from *Alice in Wonderland.*

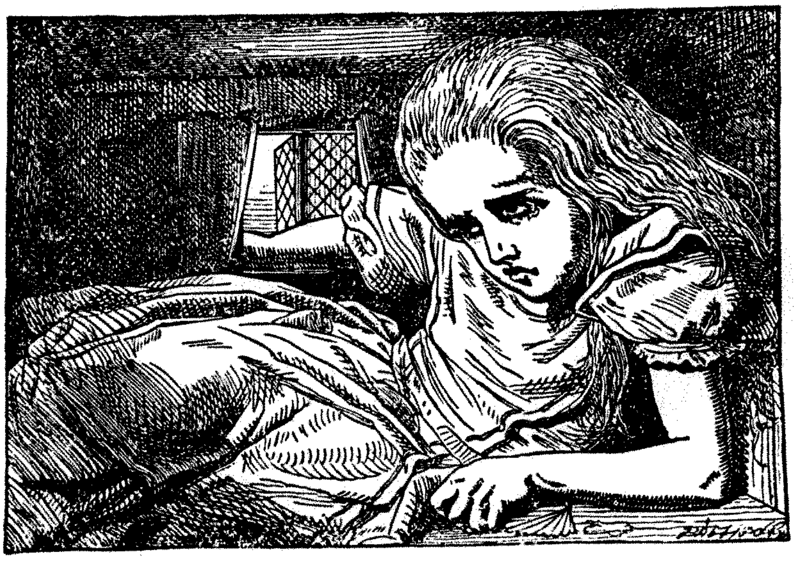

Fig 2.—Lippman's patient 2 indicated she "feels that her body is growing larger and larger until it seems to occupy the whole room." This description matches this original illustration from *Alice in Wonderland.*

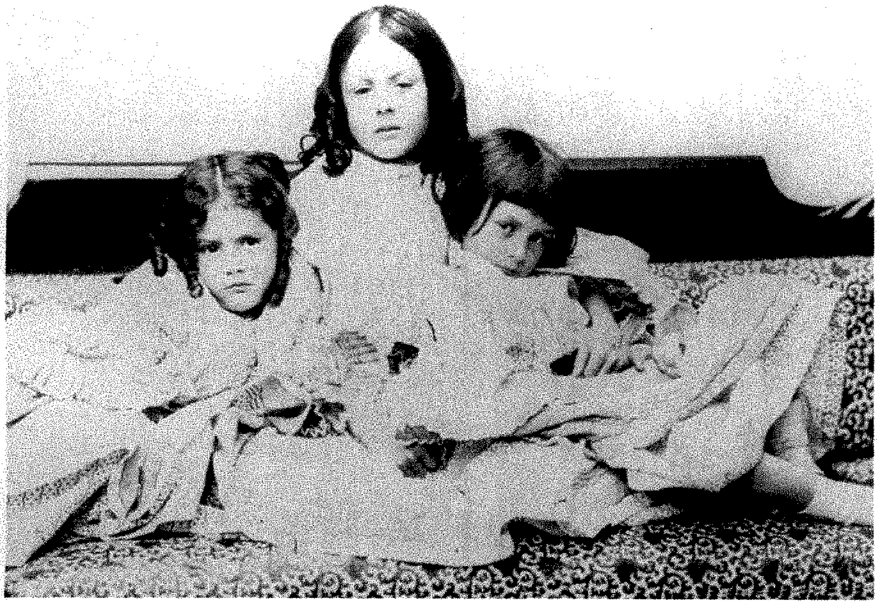

Fig 4.—A photograph by Charles Dodgson (pseudonym, Lewis Carroll) of the Liddell sisters. From left to right, Alice (the heroine of the books), Lorina, and Edith.

"Drink Me," which she does, causing her to shrink. Soon after, she eats a piece of cake marked "Eat me" and begins to grow. Alice's size continues to fluctuate through a series of adventures with the Mad Hatter, the Cheshire Cat, the Walrus, the Carpenter, and other characters. Figures 2 and 3 are reproductions of the original drawings by Sir John Tenniel for the first edition of *Alice in Wonderland* in 1865, illustrating some of these body distortions. The figure legends are exact quotes from the patients in Lippman's original article, juxtaposed with the illustrations to show how perfectly the medical syndrome he described fits the literary source.

Dodgson knew many men from upper-class Victorian society, including many physicians. His interests in medical matters and in children joined in his will, in which he left a provision, still maintained today, for perpetual endowment of a bed in The Children's Hospital, London, England. His enjoyment of children prompted him to write books for them, and "Alice" in Wonderland was a real person—Alice Liddell, the daughter of his dean at Oxford University (Fig 4).

We know that Dodgson suffered from classic migraine headaches, which he described as "bilious headaches," preceded by eye disturbances and fortification scotomas. Although his diaries do not mention headaches until many years after the *Alice in Wonderland* books were published and never relate any body image hallucinations,[7] some authors speculate that Dodgson may have experienced body distortions as a feature of his own migraines and that "Alice trod the paths of a wonderland well known to her creator."[2]

References

1. Todd J. The syndrome of Alice in Wonderland. *Can Med Assoc J.* 1955;73:701-704.
2. Lippman CW. Certain hallucinations peculiar to migraine. *J Nerv Ment Dis.* 1952;116:346-351.
3. Copperman SM. 'Alice in Wonderland' syndrome as a presenting symptom of infectious mononucleosis in children. *Clin Pediatr (Phila).* 1977;16:143-146.
4. Golden GS. The Alice in Wonderland syndrome in juvenile migraine. *Pediatrics.* 1979;63:517-519.
5. Carroll L. *Alice's Adventures in Wonderland.* London, England: Chadwick and Sons; 1865.
6. Fisher J. *The Magic of Lewis Carroll.* London, England: Bramdall House; 1973.
7. Murray TJ. The neurology of Alice in Wonderland. *Can J Neurol Sci.* 1982;9:453-457.

Central Nervous System Germinomas

A Review

Michael Bruce Horowitz, MD, Walter A. Hall, MD

• The germinoma represents a less malignant form of germ cell tumor. Depending on the individual's age, this neoplasm constitutes approximately 0.1% to 3.4% of all intracranial tumors. The embryologic origin remains a mystery; however, current theories implicate an aberration in primordial germ cell migration. Clinical presentation depends on tumor location and may involve endocrine, hypothalamic, visual, and cognitive dysfunction. In evaluating midline intracerebral masses, it is imperative that one be aware of the various radiologic appearances, endocrinologic changes, and chemical markers that help to distinguish germinomas from other neoplasms that appear in the pineal, suprasellar, and periventricular regions. Only through the careful evaluation of all available studies can the physician institute appropriate therapies such as biopsy, radiation, and chemotherapy. This article focuses on the epidemiology, embryology, clinical presentation, means of diagnosis, treatment, and outcome of this rare neoplasm.

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The germ cell tumor, a rare finding in the neuraxis, represents a neoplasm that, if properly diagnosed and managed, can be eradicated or controlled in the adult and pediatric populations.[1,2] Under this broad category, in order of frequency of appearance in the central nervous system in all age groups, lie the subcategories of germinoma (40%); mixed tumor (30%); teratoma (20%); and yolk sac tumor, embryonal carcinoma, and choriocarcinoma (10%).[2] These neoplasms most often involve the reproductive organs but may also appear in extragonadal sites such as the sacrococcygeal region, intracranial region, abdomen, retroperitoneum, thoracic cavity, pharynx, neck, thyroid, spinal cord, meninges, bladder, prostate, and soft tissues of the occipital region. Germ cell tumors arising within the ovary rarely occur before the fifth year of life. In contrast, testicular germ cell tumors are frequently found before the fifth year of life and present as a painless mass with an associated hydrocele. Pure germinomas are rare in children younger than 5 years.[1]

Pure germ line tumors are called germinomas. Differentiated germ cell tumors may be divided into embryonic (embryonal carcinoma and mature or immature teratoma) and extraembryonic (choriocarcinoma and yolk sac or endodermal sinus tumors) growths. When organized according to increasing malignant potential, these tumors are germinoma, teratoma, embryonal carcinoma, embryonal sinus tumor, and choriocarcinoma.[3] Each tumor represents the malignant correlate of a normal stage of embryonic development.[3] Germinomas arise from the primordial germ cell; teratomas arise from the differentiated embryonic cell layers; embryonal carcinoma develops from a pluripotential cell of the embryo proper; endodermal sinus tumors represent tissue from extraembryonic yolk sac endoderm; and choriocarcinoma arises from extraembryonic trophoblastic tissue.[3] This article focuses on the epidemiology, embryology, clinical presentation, means of diagnosis, treatment, and outcome of a rare treatable neoplasm, the germinoma.

EPIDEMIOLOGY

The incidence of germinomas varies among Asia, Europe, and the Western Hemisphere. Depending on an individual's age, germinomas constitute 0.1% to 3.4% of all intracranial tumors.[1,3-5] The Armed Forces Institute of Pathology reported that germ cell tumors represented 1.8% of primary intracranial tumors in individuals younger than 20 years, and germinomas represented 16.7% of these tumors.[6] Other reports indicate that germ cell tumors represent 6.5% of intracranial tumors seen during the first two decades of life.[6] Studies evaluating individuals of all ages, however, have shown germinomas to represent up to 65% of intracranial germ cell tumors.[3] The incidence of germ cell tumors in Japan far exceeds that found in other nations. A review of 20 192 brain tumors in Japan between 1969 and 1978 revealed 435 germinomas (2.7%) in all age groups, 184 of which were in children (7.8% of primary pediatric brain tumors).[7] Other series report that 0.3% to 9.4% of intracranial neoplasms in Japan are germinomas.[3-5] Just as it appears that there is a predilection for race, there also seems to be a tendency for these tumors to develop in males. Germ cell tumors have a male-female ratio of 2.24:1, while germinomas have a male-female distribution of 1.88:1.[3]

EMBRYOLOGY

Germ cell tumors arise because of neoplastic changes during embryonic development. Intracranial germ cell tu-

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mors occur in the pineal region, suprasellar-retrochiasmal area, pituitary fossa, posterior third ventricle, interpeduncular and quadrigeminal plate region, cerebellar vermis, thalamus, and walls of the lateral and third ventricles.[8] How these neoplasms come to develop in the various intracranial sites is not known.

Mature male and female germ cells are derived from primordial germ cells that appear in the yolk sac wall at the end of the third week of development.[9] The development and migration of these cells has been studied in a variety of organisms. In ascarides and in insects, at the point of the first egg division, long V-shaped chromosomes are found in blastomeres giving rise to germ cells. Blastomeres destined to become somatic cells contain fragmented versions of these chromosomes. In birds and reptiles, primordial germ cells are located in the extraembryonic blastoderm. These cells migrate into spaces between endoderm and mesoderm, penetrate blood vessels of the area vasculosa, and eventually reach the germinal ridges. Cells that stray during migration later degenerate.[10,11] In man, the origin of primordial germ cells in the embryo has not been studied. These cells are located in the endodermal epithelium of the yolk sac near the allantoic stalk. From here, cells migrate into the adjoining mesenchyme and eventually settle in the germinal ridges.[10]

Primitive germ cells arise from endoderm, migrate into adjacent mesoderm, stimulate blood vessel formation, and disseminate throughout the embryo.[8] Work performed in birds and reptiles has led to the idea that intracranial germinomas develop secondary to circulatory dispersion of cells in the embryo. An alternative theory, proposing that intracranial germinomas arise from misplaced multipotential fragments of the embryonic primitive streak, was supported by the close proximity of the most rostral portion of the primitive streak to the pineal anlage.[2,8-11] Hypothalamic and retrochiasmal tumors are not explained by this theory. Jennings et al[3] stated that the appearance of the ventral hypothalamus at 35 to 38 days coincided with the major migration phase of human germ cells. The presence of germ cell tumors in diencephalic loci suggested that local ontogenic, synaptic, and functional interrelationships may exist between the developing diencephalic structures, the pineal gland, the suprasellar region, and germ cells.[3]

CLINICAL PRESENTATION

Signs and symptoms associated with germinomas most commonly include diabetes insipidus (41%), visual field defects (33%), and hypothalamic/pituitary dysfunction (33%). Pituitary/hypothalamic abnormalities include delay or regression of sexual development (16%); hypopituitarism (16%); growth failure (9%); precocious puberty (5%); fluctuations in blood pressure, heart rate, respiration, and temperature; gastric motility; and alterations in memory, mood, appetite, and emotional behavior. Additional clinical features associated with germinomas are hydrocephalus (21%), obtundation (15%), Parinaud's syndrome (14%), pyramidal tract signs (14%), ataxia (9%), diplopia (10%), seizures (3%), choreoathetosis (2%), dementia (2%), and psychosis (1%).[2,3] Pineal region tumors generally present first with Parinaud's syndrome and hydrocephalus, while suprasellar tumors present with endocrinopathy, visual loss, and diabetes insipidus.[12]

Germinomas disseminate from the suprasellar and pineal regions by direct infiltration or spread along cerebrospinal fluid pathways.[3] Distant sites of spread include the cavernous sinus,[13] hypothalamus,[3,12] thalamus,[12,14,15] basal ganglia,[12,14-15] septum pellucidum,[12] ventricular system near the foramen of Monro and the trigone of the lateral ventricle,[15] parietal region,[17] cerebellar vermis,[15] frontal lobe,[15] and paraventricular region.[15] Cavernous sinus involvement[13] presents with headache, decreased visual acuity, third nerve palsy, orbital pain, complete ophthalmoplegia, and facial numbness. Coffey[12] described a 24-year-old woman with a hypothalamic germinoma who had anterograde and retrograde amnesia, hyperphagia, visual obscurations, headache, and normal endocrine function. Damage to the fornix, mamillothalamic tracts, and ventromedial thalamus was presumably responsible for the patient's symptoms.

Ono et al[14] described eight patients with germinomas of the thalamus and basal ganglia (third most common site of occurrence). These patients presented with hemiparesis (100%), mental disturbance (63%), increased intracranial pressure (38%), and progressive dystonia with involuntary movements (25%). Tumor affecting the cerebellum can cause dizziness, tinnitus, and gait abnormality.[15]

The endocrinologic presentation and evaluation of germinomas is an interesting and important topic. With proper diagnostic testing and institution of appropriate treatment, the patient can be returned to normal hormonal balance. Multiple endocrine abnormalities may develop as a consequence of tumor infiltration. Because of this infiltration, germinomas have a greater incidence of endocrinopathy than do craniopharyngiomas.[18] Diabetes insipidus with polyuria and polydipsia occurs in 93% of suprasellar germinomas and in 41% of germinomas, regardless of location.[3,16] Growth hormone release is impaired earlier than gonadotropin release. Low levels of luteinizing hormone and follicle-stimulating hormone and poor response to luteinizing hormone–releasing hormone have been seen. Thyroid-stimulating hormone and adrenocortical hormone are less frequently affected. Some studies have shown delayed and/or exaggerated plasma thyroid-stimulating hormone response to thyroid-releasing hormone. In these patients, despite an elevated level of thyroid-stimulating hormone, a hypothyroid state often exists because the thyroid-stimulating hormone is biologically less active.[18] For unknown reasons, adrenocortical hormone response to exogenous corticotropin-releasing factor is often delayed in persons with hypothalamic germinomas.[18] Growth hormone release in response to exogenous gonadotropin-releasing factor is another indicator of hypothalamic invasion.[18] With hypothalamic destruction or interruption of the hypothalamic-pituitary axis, prolactin secretion is increased. Despite an increase in prolactin, galactorrhea may not be seen with hypothalamic destruction due to an absence of sex hormones crucial for milk production.[4,18]

Germinomas may have their course complicated by other extracranial manifestations such as genetic abnormalities and metastases. Two genetic diseases seen with germinoma are Klinefelter's syndrome and de Lange's syndrome. Klinefelter's syndrome, originally described in 1942, affects 0.6% of live male neonates and is characterized by gynecomastia, small atrophic testicles, absent spermatogenesis, high urinary excretion of gonadotropins, and eunuchoid habitus.[19] This syndrome has a high association with breast cancer, lymphoma, leukemia, transitional cell carcinoma of the bladder, and prostatic cancer and was first associated with extragonadal germ cell tumors in 1972. Germinoma and choriocarcinoma have both been associated with Klinefelter's syndrome. An alteration in gonadal ridge differentiation leading to malinduction and dyssynchronization of migration of primordial germ cells may explain the association between these maladies.[20-22] De Lange's syndrome was first described in 1933 in two infants with mental retardation, delayed growth and development, short stature, low body weight, bushy eyebrows fused at the midline, long upturned eyelashes, small nose with a low bridge, anteverted nostrils, crescent-shaped mouth, hirsutism, hypoplastic nipples and umbilicus, proximally implanted thumbs, bilateral simian creases, flexion contractions of the elbows, and decreased quantity of pubic hair.[23]

Although intracranial germinomas rarely spread outside the central nervous system, there have been reported cases of distal metastases, mostly from pineal lesions.[24] Because pineal metastases predominate, extracranial metastases from a suprasellar germinoma should suggest that the original tumor contained foci of more malignant germ cell elements.[24] Metastatic sites include lung, kidney, bladder, mediastinum, paratracheal lymph nodes, breast, peritoneum, bone, skin, stomach, small bowel, mesentery, and diaphragm.[24-27] Although peritoneal, pulmonary, and cardiac metastases have been reported in patients without spinal fluid shunting devices, they have been speculated to occur in patients with such systems as a result of seeding from the central nervous system cavity.[25,28,29]

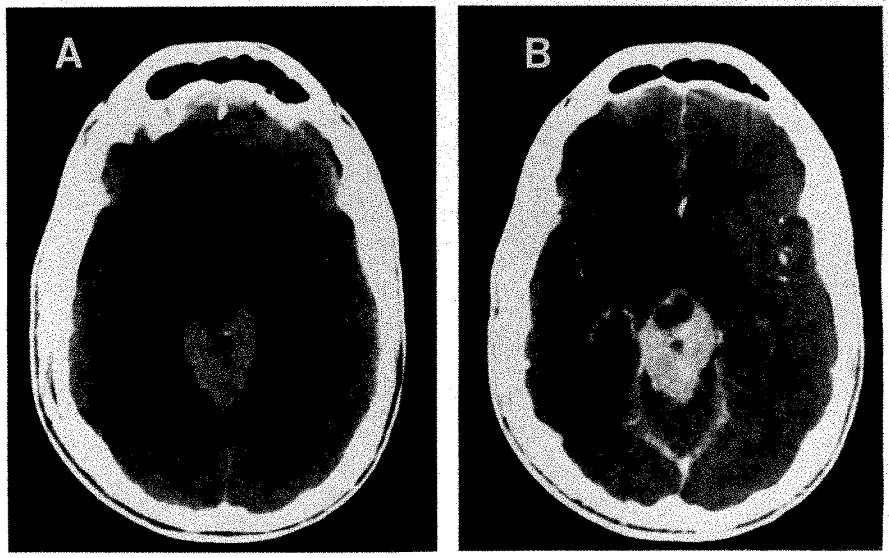

Fig 1.—A, Nonenhanced computed tomographic image of a pineal region germinoma (General Electric Model 9800). Notice increased density in relation to surrounding brain tissue and the presence of intratumoral cysts. B, Contrast-enhanced computed tomographic scan (Isovue 300, Squibb Diagnostics, New Brunswick, NJ).

DIAGNOSIS

Radiologic Evaluation

When the findings of the neurologic examination are abnormal, computed tomography or magnetic resonance imaging is usually the first diagnostic test that is performed. Ganti et al[30] evaluated 16 pineal germinomas by computed tomography and found that 94% percent were denser than brain on unenhanced computed tomographic scan, 88% showed moderate to marked contrast enhancement, 38% showed prominent and slightly enlarged pineal calcification, 63% showed parenchymal calcification with a coarse nodular pattern, and 32% showed meningeal and ependymal seeding. Kageyama et al[31] describe three types of pineal calcifications. Type 1 involves tumor within and around the calcified pineal body. There is no capsule between the mass and the surrounding brain. Type 2 represents several calcified areas that, following radiotherapy, form a single mass. This lesion most likely represents encapsulated tumor growing within the pineal body. Type 3 calcifications appear after radiotherapy. Their pathogenesis remains uncertain; however, they most likely represent intrapineal tumor. Abu-Yousef and Hitchon,[32] in three patients with germinoma, found no evidence of abnormal calcification. Other studies have emphasized the occasional presence of hemorrhage.[33]

While moderate inhomogeneous enhancement after administration of contrast is possible, nonhomogeneous enhancement should suggest another type of lesion.[34,35] An irregular border may represent infiltration.[35] In contrast to germinomas, teratomas are sharply demarcated from the surrounding brain, contain fat, have no significant contrast enhancement, may be cystic, and exhibit linear and nodular calcific deposits on computed tomograms.[30] Cysts may also be found with germinomas and are thought to represent proteinaceous fluid or liquified necrosis (Fig 1).[32] Embryonal cell carcinoma and choriocarcinoma are hyperdense before contrast administration, enhance markedly, and exhibit no abnormal pineal or parenchymal calcification.[30]

Basal ganglia and thalamic germinomas may be associated with ipsilateral cerebral hemiatrophy.[33,36] Wallerian degeneration secondary to the destruction of subcortical structures may be responsible for this wasting.[33] Chang et al[35] state that germinomas in the basal ganglia and thalamus are irregular and demonstrate intratumoral cysts and calcification.

Magnetic resonance imaging represents another method of evaluation. On both long and short repetition time spin echo series in four patients reviewed by Kilgore et al,[37] the signal from germinomas was isodense in comparison with normal brain. The tumor can displace cerebrospinal fluid (CSF) and adjacent structures such as the quadrigeminal plate, sylvian aqueduct, and posterior third ventricle.[37] Germ cell tumors with embryonal cell elements had long T_1- and T_2-weighted signals.[37] Magnetic resonance imaging offers the advantage of easily acquiring images in the coronal and sagittal planes. The disadvantage is the inability to image calcium.

Markers

Cerebrospinal fluid examination for cytologic and marker studies is useful in the evaluation of a patient with a suspected germ cell tumor if samples can be obtained without precipitating herniation. Elevated levels of human chorionic gonadotropin (HCG) and α-fetoprotein (AFP) are more closely correlated with malignant germ cell tumors such as embryonal carcinoma, endodermal sinus tumors (yolk sac tumors), and choriocarcinoma,[2,38-40] with HCG and AFP elevated in the former two and HCG alone elevated in the latter. The level of HCG is only occasionally elevated with germinomas, while the level of AFP is rarely elevated. α-Fetoprotein is usually more specific for highly malignant neoplasms, and HCG is associated with more benign neoplasms, although it can be produced by the most malignant masses. Recently, it has been proposed that absolute levels of AFP should not be used, but rather an AFP index calculated as (CSF/serum AFP)/(CSF/serum albumin), with a value greater than 1.42 indicating local synthesis of AFP in the central nervous system.[41] When present, markers are a useful indicator of tissue type; however, CSF marker levels are not elevated in 10% to 20% of the more malignant germ cell tumors.[38] Measurement of AFP is often unreliable

(1) because there is cross-reactivity of the assay with other CSF proteins, (2) because there is evidence that three types of human AFP exist (one of which may be a normal CSF component), and (3) because many normal individuals and individuals with nonmalignant conditions have elevated levels of AFP.[41] In addition to helping the physician diagnostically, marker levels can be used to evaluate the effectiveness of treatment. Anecdotal reports state that a lack of return of markers to normal levels after treatment indicates a poor prognosis.[38]

Markers other than AFP and HCG have recently been associated with germinomas. The level of angiotensin I–converting enzyme was elevated in the plasma of one patient with a suprasellar germinoma who did not have sarcoid, granulomatous disease, hyperthyroidism, or diabetes, diseases commonly associated with elevated levels of this enzyme. Angiotensin I–converting enzyme was also found in tumor cells obtained by biopsy.[42] Interestingly, an isomeric form of kidney and lung angiotensin I–converting enzyme is present in normal testes and sperm. Another marker, placental alkaline phosphatase was recently found to be associated with germinoma.[5,39] In the past, elevated levels of this enzyme were associated with pregnancy, testicular seminoma, and ovarian, lung, breast, pancreatic, and adrenal cancers.[5,39] Shinoda et al[39] found levels of serum placental alkaline phosphatase that were less than 0.2 IU/mL in patients with teratoma, metastatic choriocarcinoma from the testis, glioma, meningioma and acoustic neurilemoma. Three patients with germinoma had serum levels ranging from 0.52 to 3.78 IU/L, and two had elevated CSF values of 0.83 and 9.83 IU/L (normal, <0.20 IU/L in serum and <0.11 IU/L in CSF). Melatonin has been studied in patients with pineal region tumors. Low melatonin levels are associated with pineal destruction, and high levels suggest the presence of a melatonin-secreting neoplasm. An increase in melatonin has been seen with germinoma. Some argue that such elevation is a consequence of laboratory error.[43]

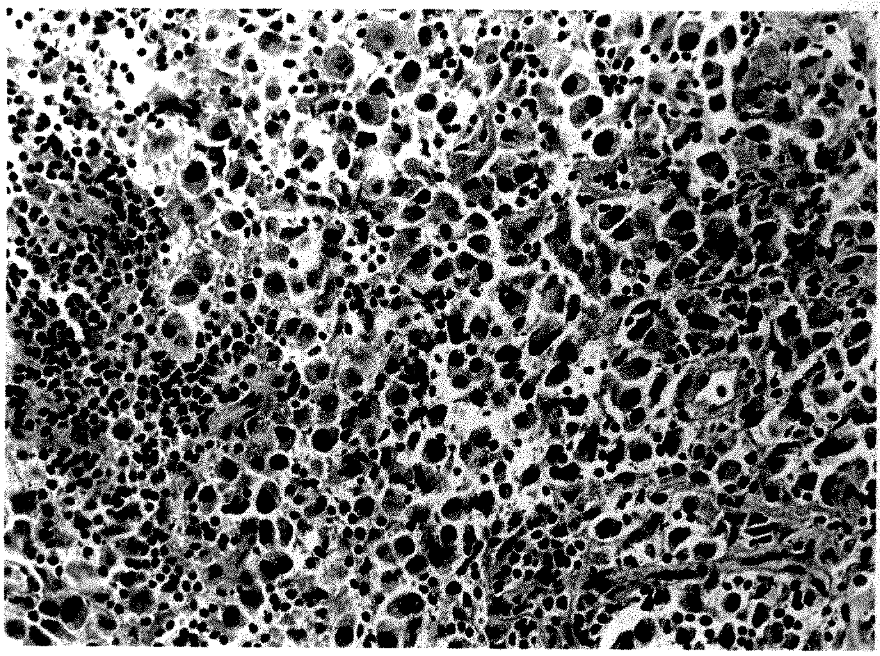

Fig 2.—Microscopic image of a germinoma demonstrating two cell populations. The first consists of large cells with well-defined cell borders, large nuclei, and prominent nucleoli. The second consists of small, round tumor-infiltrating lymphocytes. Occasional mitoses can be seen (hematoxylin-eosin, ×250).

HISTOPATHOLOGIC EXAMINATION

Germinomas characteristically infiltrate locally and spread by dissemination through the craniospinal and subarachnoid spaces. Parenchymal metastases and extradural spread are rare.[40] Grossly, solid tumor tissue can be soft and purplish-gray.

Microscopically, these tumors consist of large polygonal cells surrounded by fibrous connective tissue. Lymphocytic infiltration is most prominent around blood vessels. Cells tend to organize in sheets and lobules and are characterized by large round or oval vesicular nuclei, prominent irregular nucleoli, pale ill-defined cytoplasm, rich stores of glycogen, and coarse or fine granular chromatin.[15,24,27,44,45] Mitotic figures can be present (Fig 2).[24,44]

Ultrastructurally, germinomas display scanty cytoplasm, few organelles, and abundant glycogen. The cytoplasm contains poorly developed Golgi complexes, distorted and aggregated mitochondria, and moderately developed rough and smooth endoplasmic reticulum. Cell membranes are occasionally fused by desmosomes or tight junctions.[15,44] An additional interesting finding is that of intranuclear membranes, structures adjacent to electron-lucent spaces measuring 20 to 100 nm in width and 3 μm in length. Thick layers of chromatin surround these membranes, which are arranged parallel, perpendicular, or oblique to the nuclear envelope. Such structures are sometimes interrupted at regular intervals and occasionally are contiguous with the nuclear envelope over a 20- to 100-nm distance. The significance of these intranuclear membranes is unknown, yet a role in nucleocytoplasmic material exchange has been suggested. They may also be involved with accelerated protein synthesis or abnormal DNA metabolism.[46]

Lymphocytic infiltration of germinomas has been demonstrated by light and electron microscopy. Tumor-infiltrating lymphocytes have been characterized using monoclonal antibodies. In intracranial germinomas, 70% to 80% of tumor-infiltrating lymphocytes were T lymphocytes, and the remainder were B lymphocytes. Cytotoxic/suppressor and helper/inducer T-cell types were intermingled.[47] Cravioto and Dart[48] and Hassoun et al[49] have speculated on the significance of lymphocytes within a tumor. They believe that the activity of tumor-infiltrating lymphocytes may represent a host immunologic response to tumor antigens.

TREATMENT

Past surgical treatment of germinomas by open biopsy or resection was fraught with danger, especially prior to the advent of microsurgical technique. The 30% to 70% morbidity associated with biopsy prompted Torkildsen in 1948 to propose empiric shunting and irradiation for suspicious lesions.[50] More recently, neurosurgeons have relied on other modes of therapy to diagnose and manage this type of germ cell tumor.

Computed tomographic–guided stereotaxis is now an accepted method for obtaining diagnostic tissue. This procedure can provide a sample within 1 to 3 mm of a desired target. However, because the average sample size is 2 to 4 mm in greatest diameter, sampling error can occur when a heterogeneous tumor is encountered.[51] Nevertheless, stereotactic surgery, with a 0% to 0.5% morbidity, provides a safe method of sampling deep intracranial tissues.[50] Linstadt et al[52] followed up 33 patients with germinoma for a median of 5.3 years (range, 0.1 to 27.5 years). At 5 years, all patients with stereotactic biopsy-proved germinomas were alive, while only 73% of the patients who did not undergo biopsy were alive after the same period. An initial incorrect diagnosis was believed to be responsible for this difference, since 66% of those with recurrent disease were found to harbor an ependymoma or a pinealoblastoma. Biopsy, therefore, may increase survival by increasing diagnostic accuracy and as a result allow for the institution of proper therapy.[52]

The extreme radiosensitivity of germinomas has led some to initiate radiation therapy of suspected lesions without a tissue diagnosis. Biopsy studies, however, have shown that only 61% of lesions suspected to be of germ cell origin on the basis of imaging studies will actually be germ cell tumors.[50] Fifteen percent will be of pineal parenchymal origin (pineocytoma or pinealoblastoma), 17% will be gliomas, and 7% will represent other lesions.[50] Tumor regression after a maximum dose of 2000 cGy supports the presence of a germinoma.[34] Tumors that do not respond to such doses may represent mixed tumors, choriocarcinomas, embryonal carcinomas, endodermal sinus tumors, pinealomas, teratomas, and glial tumors. Pinealoblastoma and histiocytosis may respond to radiation treatment.[53]

Radiation regimens for germinoma therapy vary. Most studies recommend 4000 to 6000 cGy to the primary intracranial site[52,54-56] and approximately 3000 cGy to the remainder of the uninvolved brain.[54,56] Recurrence-free rates are reported to be 85% to 100% at 5 to 10 years posttreatment.[50] Local control appears to improve from about 50% with 40 Gy or less to 90% with 50 Gy or more.[50] Some investigators believe that spinal irradiation should be reserved (1) for lesions that demonstrate clear CSF invasion by myelography, cytology, magnetic resonance imaging, or computed tomography; (2) for extensive intracranial disease; (3) for multiple foci of tumor; (4) for ventricular or meningeal seeding; and (5) after tumor spillage at surgery.[50] Cerebrospinal fluid invasion can be expected in 6% to 85% of patients with histologically proved germinomas.[52-55,57] In such situations, dosages vary between 3600 and 4500 cGy.[53,55] Controlled prospective studies have not been performed to determine the value of adjuvant spinal irradiation.[52] Linstadt et al[52] claimed that 8% of their study patients who underwent radiation therapy to the cord developed spinal metastases, while 23% of those who did not undergo radiation therapy developed metastases. In their minds, the 15% benefit provided by radiation therapy did not justify the attendant risks, such as growth retardation and myelitis.[52] Shibamoto et al[56] further complicated the decision-making process by citing their findings in which six patients had positive CSF cultures, did not receive spinal irradiation, and had no spinal involvement over a 6- to 12-year follow-up period. These favorable outcomes may be secondary to decreased viability of free-floating cells or irradiation of cells as they circulate within the CSF and enter an irradiated field.[48] Nevertheless, despite their observations, Shibamoto and colleagues recommend radiation therapy for all individuals with evidence of spinal compartment involvement.

Despite the efficacy of radiation therapy in the treatment of germinomas, chemotherapy has recently been advocated as an adjuvant therapy to decrease the total dose of radiation necessary to induce tumor resolution. This would be especially useful for germinomas in areas where radiation therapy could cause endocrinopathies, cognitive deficits, or other untoward side effects.[58-60] Allen et al[58] described the use of two courses of cyclophosphamide administered as 900 mg/m^2 over 2 days (1800 mg/m^2 total). A complete response to chemotherapy was reinforced by 3000 cGy over 4 weeks, while less than complete resolution was coupled with 5000 cGy over 5 to 6 weeks in 160- to 180-Gy fractions.[58] If the neoplasm was disseminated, spinal irradiation was added. Ninety-one percent of patients had complete resolution and 9% had total regression of the intracranial mass with subsequent positive CSF cytologic studies. Disease-free survival ranged from 23 to 89 months. Complications included neutropenia secondary to marrow toxicity. As a consequence of their findings, Allen and colleagues recommended that the following protocol be carried out when treating any germ cell tumor: (1) biopsy; (2) staging by computed tomography, myelography, CSF markers, and magnetic resonance imaging; (3) chemotherapy; and (4) radiation therapy.

An alternate chemotherapy regimen for the treatment of initial, recurrent, and metastatic germinomas includes bleomycin, cisplatin, and vinblastine sulfate or cisplatin and etoposide.[60-64] The former involves the same chemotherapeutic combination used for testicular tumors. Pharmacokinetic studies have shown significant CSF penetration by cisplatin and bleomycin, but not by vinblastine.[61] Blood-brain barrier penetration is apparently made possible by effects from previous irradiation and/or tumor factors.

As a consequence of improved means of diagnosis and innovative therapies, the current survival rate for patients with germinoma ranges from 66% to 86% after a median follow-up of 5 years or longer.[65] It is these results that make germinomas rewarding tumors to treat, for with proper early diagnosis and appropriate treatment, the patient, who is most often a child, can return to a normal life-style with minimal to little deficit.

References

1. Rudolph AM, Hoffman JE. *Pediatrics.* 18th ed. East Norwalk, Conn: Appleton & Lange; 1987.
2. Butler IJ, Borit A. Germ cell tumors of the diencephalon. In: *The Pineal and Its Hormones.* New York, NY: Alan R Liss Inc; 1982: 263-271.
3. Jennings MT, Gelman R, Hochberg F. Intracranial germ-cell tumors: natural history and pathogenesis. *J Neurosurg.* 1985;63:155-167.
4. Buchfelder M, Fahlbusch M, Walther M, Mann K. Endocrine disturbances in suprasellar germinomas. *Acta Endocrinol (Copenh).* 1989;120:337-342.
5. Shinoda J, Miwa Y, Sakai N, et al. Immunohistochemical study of placental alkaline phosphatase in primary intracranial germ-cell tumors. *J Neurosurg.* 1985;63:733-739.
6. Rueda-Pedraza M. Primary intracranial germ cell tumors in the first two decades of life. *Perspect Pediatr Pathol.* 1987;10:160-207.
7. Sano K. A statistical study of brain tumors in Japan: general features. *Jpn J Clin Oncol.* 1986;17:19-28.
8. Walsh JW. Suprasellar germinomas. In: Wilkins WH, Rengachary SS, eds. *Neurosurgery.* New York, NY: McGraw-Hill International Book Co; 1985:921-925.
9. Langman J. Gametogenesis. In: *Medical Embryology.* 4th ed. Baltimore, Md: Williams & Wilkins; 1981:1-16.
10. Balinsky BI, Fabian BC. *An Introduction to Embryology.* 4th ed. Philadelphia, Pa: WB Saunders Co; 1975:457-523.
11. Sano K, Matsutani M, Seto T. So-called intracranial germ cell tumors: personal experience and a theory of their pathogenesis. *Neurol Res.* 1989;11:118-126.
12. Coffey RJ. Hypothalamic and basal forebrain germinoma presenting with amnesia and hyperphagia. *Surg Neurol.* 1989;31:228-233.
13. Poon W, Ng HK, Wong K, South JR. Primary intrasellar germinoma presenting with cavernous sinus syndrome. *Surg Neurol.* 1988;30:402-405.
14. Ono N, Inoue HK, Naganuma H, Kunimine H, Zama A, Tamura M. Diagnosis of germinal neoplasm in the thalamus and basal ganglia. *Surg*

Neurol. 1986;26:24-28.

15. Masuzawa T, Shimabukuro N, Nakahara H, Sato I, Sato F. Germ-cell tumors (germinoma and yolk sac tumor) in unusual sites in the brain. *Clin Neuropathol*. 1986;5:190-202.

16. Fujieda K, Matsuura N, Mikami Y, et al. Endocrine function and growth in children with CNS tumors—with special emphasis on germinoma. *Acta Paediatr Jpn*. 1988;30(suppl):61-67.

17. Nakano S, Hisao U, Kinoshita K. Unusual clinical presentation of a presumed pineal germinoma with two disseminated lesions. *Neurosurgery*. 1988;23:235-236.

18. Imura H, Kato Y, Nakai Y. Endocrine aspects of tumors arising from suprasellar, third ventricular regions. *Prog Exp Tumor Res*. 1987;30:313-324.

19. Nora JJ, Fraser FC. *Medical Genetics: Principles and Practice*. 2nd ed. Philadelphia, Pa: Lea & Febiger, 1981.

20. Arens R, Marcus D, Engelberg S, Findler G, Goodman R, Passwell JH. Cerebral germinomas and Klinefelter syndrome. *Cancer*. 1988;61:1228-1231.

21. Ellis SJ, Crockard A, Barnard RO. Klinefelter's syndrome, cerebral germinoma, Chiari malformation, and syrinx: a case report. *Neurosurgery*. 1986;18:220-222.

22. Lee LW, Stephens RL. Klinefelter's syndrome and extragonadal germ cell tumors. *Cancer*. 1987;60:1053-1055.

23. Sugita K, Izumi T, Yamaguchi K, Fukuyama Y, Sato A, Kajita A. Cornelia de Lange syndrome associated with a suprasellar germinoma. *Brain Dev*. 1986;8:541-546.

24. Jennings CD, Powell DE, Walsh JW, Mortara RH. Suprasellar germ cell tumors with extracranial metastases. *Neurosurgery*. 1985;16:9-12.

25. Levin CV, Rutherfoord GS. Metastasizing pineal germinoma. *S Afr Med J*. 1985;68:36-39.

26. Gay CJ, Janco RL, Lukens NJ. Systemic metastases in primary intracranial germinoma. *Cancer*. 1985;55:2688-2690.

27. Kim K, Koo BC, Delaflor R, Shaikh BS. Pineal germinoma with widespread extracranial metastases. *Diagn Cytopathol*. 1985;1:118-122.

28. Woo E, Yu YL. Isolated hypoglossal nerve palsy due to metastatic germinoma in the neck: a ventriculoatrial shunt-related complication. *Neurosurgery*. 1988;23:237-240.

29. Talamo TS, Mendelow H. Primary intracranial germinoma with massive ventriculoperitoneal shunt metastases. *J Surg Oncol*. 1985;28:39-41.

30. Ganti SR, Hilal SK, Stein BM, Silver AJ, Mawad M, Sane P. CT of pineal region tumors. *AJR Am J Roentgenol*. 1986;146:451-458.

31. Kageyama N, Kobayashi T, Kida Y, Yoshida J, Kato K. Intracranial germinal tumors. *Prog Exp Tumor Res*. 1987;30:225-267.

32. Abu-Yousef M, Hitchon PJ. The role of computed tomography in the management of pineal region tumors. *Australas Radiol*. 1984;27:284-293.

33. Mutoh K, Okuno T, Ito M, et al. Ipsilateral atrophy in children with hemispheric cerebral tumors: CT findings. *J Comput Assist Tomogr*. 1988;12:740-743.

34. Boyd MC, Steinbok P. Pineal region tumors. *Can J Neurol Sci*. 1985;12:35-38.

35. Chang T, Mu Huo Teng M, Guo WY, Sheng WC. CT of pineal and intracranial germ cell tumors. *AJNR*. 1989;10:1039-1044.

36. Soejima T, Takeshita I, Yamamoto H, Tsukamoto Y, Fukui M, Matsuoka S. Computed tomography of germinomas in basal ganglia and thalamus. *Neuroradiology*. 1987;29:366-370.

37. Kilgore DP, Strother CM, Starshak RJ, Haughton VM. Pineal germinoma: MR imaging. *Radiology*. 1986;158:435-438.

38. Edwards MSB, Davis RL, Laurent JP. Tumor markers and cytologic features of cerebrospinal fluid. *Cancer*. 1985;56:1773-1777.

39. Shinoda J, Yamada H, Sakai N, Ando T, Hirata T, Miwa Y. Placental alkaline phosphatase as a tumor marker for primary intracranial germinoma. *J Neurosurg*. 1988;68:710-720.

40. Stark E, Knehans A, Wurster U, Patzold U. Primary germinoma of the brain. *Clin Neurol Neurosurg*. 1986;88:263-265.

41. Penley WC, Grosh WW, Crean DM, Hainsworth JD, Greco FA, Parl FF. Cerebrospinal fluid alpha-fetoprotein in germ-cell neoplasms. *South Med J*. 1988;81:1195-1197.

42. Rohmer V, Saint-Andre JP, Alhenc-Gelas F, Corvol P, Bigorgne JC. Angiotensin I–converting enzyme in a suprasellar germinoma. *Am J Clin Pathol*. 1986;87:281-284.

43. Vorkapic P, Waldhauser F, Bruckner R, Biegelmayer C, Schmidbauer M, Pendl G. Serum melatonin levels: a new neurodiagnostic tool in pineal region tumors? *Neurosurgery*. 1987;21:817-824.

44. Scheithauer BW. Neuropathology of pineal region tumors. *Clin Neurosurg*. 1985;32:351-383.

45. Bjornsson J, Scheithauer BW, Okazaki H, Leech RW. Intracranial germ cell tumors: pathobiological and immunohistochemical aspects of 70 cases. *J Neuropathol Exp Neurol*. 1985;44:32-46.

46. Koide O, Iwai S, Matsumura H. Intranuclear membranous profiles in germinoma cells: a variant of nuclear pockets and intranuclear annulate lamellae. *Acta Pathol Jpn*. 1985;35:605-619.

47. Saito T, Tanaka R, Kouno M, Washiyama K, Abe S, Kumanishi T. Tumor infiltrating lymphocytes and histocompatability antigens in primary intracranial germinomas. *J Neurosurg*. 1989;70:81-85.

48. Cravioto H, Dart D. The ultrastructure of pinealoma. *J Neuropathol Exp Neurol*. 1972;32:552-563.

49. Hassoun J, Gambarelli D, Choux M, Toga M. Macroscopic activity in intracerebral germinoma: ultrastructural study of a case. *Hum Pathol*. 1980;11:207-210.

50. Dearnaley DP, A'Hern RP, Whittaker S, Bloom HJG. Pineal and CNS germ cell tumors: Royal Marsden Hospital experience 1962-1987. *Int J Radiat Oncol Biol Phys*. 1990;18:773-781.

51. Kraichoke S, Cosgrove M, Chandrasoma PT. Granulomatous inflammation in pineal germinoma. *Am J Surg Pathol*. 1988;12:655-660.

52. Linstadt D, Wara WM, Edwards MS, Hudgins RJ, Sheline GE. Radiotherapy of primary intracranial germinomas: the case against routine craniospinal irradiation. *J Radiat Oncol Biol Phys*. 1988;15:291-297.

53. Rich TA, Cassady JR, Strand RD, Winston KR. Radiation therapy for pineal and suprasellar germ cell tumors. *Cancer*. 1985;55:932-940.

54. Fields JN, Fulling KH, Thomas PR, Marks JE. Suprasellar germinoma: radiation therapy. *Radiology*. 1987;164:247-249.

55. Kersh CR, Constable WC, Eisert DR, et al. Primary central nervous system germ-cell tumors. *Cancer*. 1988;61:2148-2152.

56. Shibamoto Y, Abe M, Yamashita J, et al. Treatment results of intracranial germinoma as a function of irradiated volume. *Int J Radiol Oncol Biol Phys*. 1988;15:285-290.

57. Sakai N, Yamada H, Andoh T, Hirata T, Shimizu K, Shinoda J. Primary intracranial germ-cell tumors. *Acta Oncol*. 1988;27:43-50.

58. Allen JC, Kim JH, Packer RJ. Neoadjuvant chemotherapy for newly diagnosed germ-cell tumors of the central nervous system. *J Neurosurgery*. 1987;67:65-70.

59. Kimura E, Arita N, Hayakawa T, et al. Successful combination chemotherapy (*cis*-platinum, vinblastine, and bleomycin) against peritoneal dissemination of intracranial germ cell tumor. *Neurosurgery*. 1986;18:802-804.

60. Allen JC, Bosl G, Walker R. Chemotherapy trials in recurrent primary intracranial germ cell tumors. *J Neurooncol*. 1985;3:147-152.

61. Ginsberg S, Kirshner J, Reich S, et al. Systemic chemotherapy for a primary germ cell tumor of the brain: a pharmacokinetic study. *Cancer Treatment Rep*. 1981;65:477-483.

62. Kirshner JJ, Ginsberg S, Fitzpatrick AV, Comis RL. Treatment of a primary intracranial germ cell tumor with systemic chemotherapy. *Med Pediatr Oncol*. 1981;9:361-365.

63. Kobayashi T, Yoshida J, Ishiyama J, Satoshi N, Kito A, Kida Y. Combination chemotherapy with cisplatin and etoposide for malignant intracranial germ-cell tumors. *J Neurosurg*. 1989;70:676-681.

64. Pinkerton CR, Pritchard J, Spitz L. High complete response rate in children with advanced germ cell tumors using cisplatin-containing combination chemotherapy. *J Clin Oncol*. 1986;4:194-199.

65. Hudgins RJ, Hudgins PA. Pineal region tumors in children. *Contemp Neurosurg*. 1990;12:1-6.

Observation

Opercular Cheiro-oral Syndrome

Julien Bogousslavsky, MD; Karin Dizerens, MD; Franco Regli, MD; Paul-André Despland, MD

• Perioral and distal upper limb sensory dysfunction (cheiro-oral syndrome) has classically been attributed to cortical involvement. In previously reported cases of the syndrome, caused by stroke, however, the thalamus or brain stem has been the actual site of the lesion. We have studied two patients with infarct in the superficial middle cerebral artery territory involving the parietal operculum. Sensory involvement was purely subjective in the face, but severe hypoesthesia was present in the distal upper limb, involving mainly position sense, stereognosis, and graphesthesia. Temperature and pain sensation were involved in one patient. These findings correlated with involvement of the lower part of the postcentral gyrus, more caudal parts of the parietal operculum, and underlying white matter. This opercular cheiro-oral syndrome seems more uncommon than faciobrachiocrural hemihypesthesia associated with anterior parietal artery territory infarct. A double supply to the parietal opercular region through branches of the temporal arteries and anterior parietal artery may explain the rarity of cheiro-oral syndrome resulting from hemisphere stroke, because simultaneous and partial compromise to two different pial artery networks is uncommon.

(*Arch Neurol.* 1991;48:658-661)

The "operculum of the insula of Reil," or operculum, refers to the region that surrounds the insula (*operculum* means lid or cover). Since it is formed by part of the frontal, temporal, and parietal gyri, the operculum is usually divided into a frontal operculum, which includes the lower part of the precentral gyrus and of the posterior part of F_3, a temporal operculum, which is the rostral part of the superior temporal gyrus up to Heschl's transverse gyrus, and a parietal operculum, which includes the lower part of the postcentral gyrus and P_1, and may extend to the rostral part of P_2. While an anterior operculum syndrome due to involvement of the frontal operculum has been recognized,[1-4] the neurologic picture associated with damage to the posterior part of the operculum has not been adequately studied. We describe two patients with sensory involvement limited to the perioral region and distal part of the upper limb (cheiro-oral syndrome), in association with parietal opercular infarction.

REPORT OF CASES

CASE 1.—A 63-year-old right-handed male engineer was a cigarette smoker and had untreated hypercholesterolemia. One morning at 2 AM, he suddenly experienced a feeling of disappearance of his right forearm, associated with a decrease of touch sensation without any weakness. At the same time, he experienced tingling in the right side of his mouth. He was admitted to hospital 10 hours later. On neurologic examination, optic fundi, visual acuity, visual fields, and pupil and eye movements were normal. Facial sensation and corneal reflex were symmetrical. A slight decrease in voluntary lower facial contraction was present on the right. There was no dysarthria or dysphagia, and the palate moved symmetrically. The gag reflex was normal. The tongue protruded in the midline. Tactile, pain, and temperature sensation were normal in the face and mouth. Tendon reflexes were symmetrical. The plantar reflexes were flexor. There was a slight distal paresis in the right hand, with decreased finger motility. There was a slight pronator drift with elevation of the right arm. There was a mild difficulty in reaching objects with the right arm, without tremor or asterixis. There was no gait ataxia. Touch, pain, and temperature sensation were abolished in the right forearm. Position sensation of the fingers and wrist was abolished on the right. Stereognosis (recognition of small objects such as keys, coins, or a pin) and graphesthesia (recognition of figures drawn by the examiner on the palm of hand) were also abolished. Vibration (128 Hz) sensation was decreased (4/8) in the right wrist and hand. Neuropsychological examination with a standard battery of tests[5] did not disclose any disturbance. General examination findings were normal. The patient's blood pressure was 150/90 mm Hg. The results of standard blood tests and urinalysis were normal except for an increased cholesterol level (7.3 mmol/L). The electrocardiogram was normal. Extracranial Doppler ultrasounds were normal. Computed tomographic scans of the brain on admission were normal. Magnetic resonance imaging performed after 6 days showed a hyperintense cortical and subcortical area in the left postcentral area at the level of the parietal operculum on T_2-weighted images. The intensity was enhanced after gadolinium injection (Fig 1).

On discharge 11 days after admission, the findings of the neurologic examination had markedly improved. A slight decrease in pain and touch sensation still persisted in the fingers on the right, predominantly in the fourth and fifth fingers. Only a few disturbances in position sensation were still present, but severe stereognostic and graphesthesia disturbances persisted.

CASE 2.—On awakening one morning, a 71-year-old man experienced decrease of touch sensation in his left hand and numbness in the left side of his upper and lower lips.

He had untreated hypertension and insulin-independent diabetes. His right forearm had been amputated 22 years before as a result of a work injury. One year earlier, the patient had experienced transient weakness in the left upper limb. Computed tomography at that time showed a right frontal infarct.

On neurologic examination, the patient was alert and well orientated. Optic fundi,

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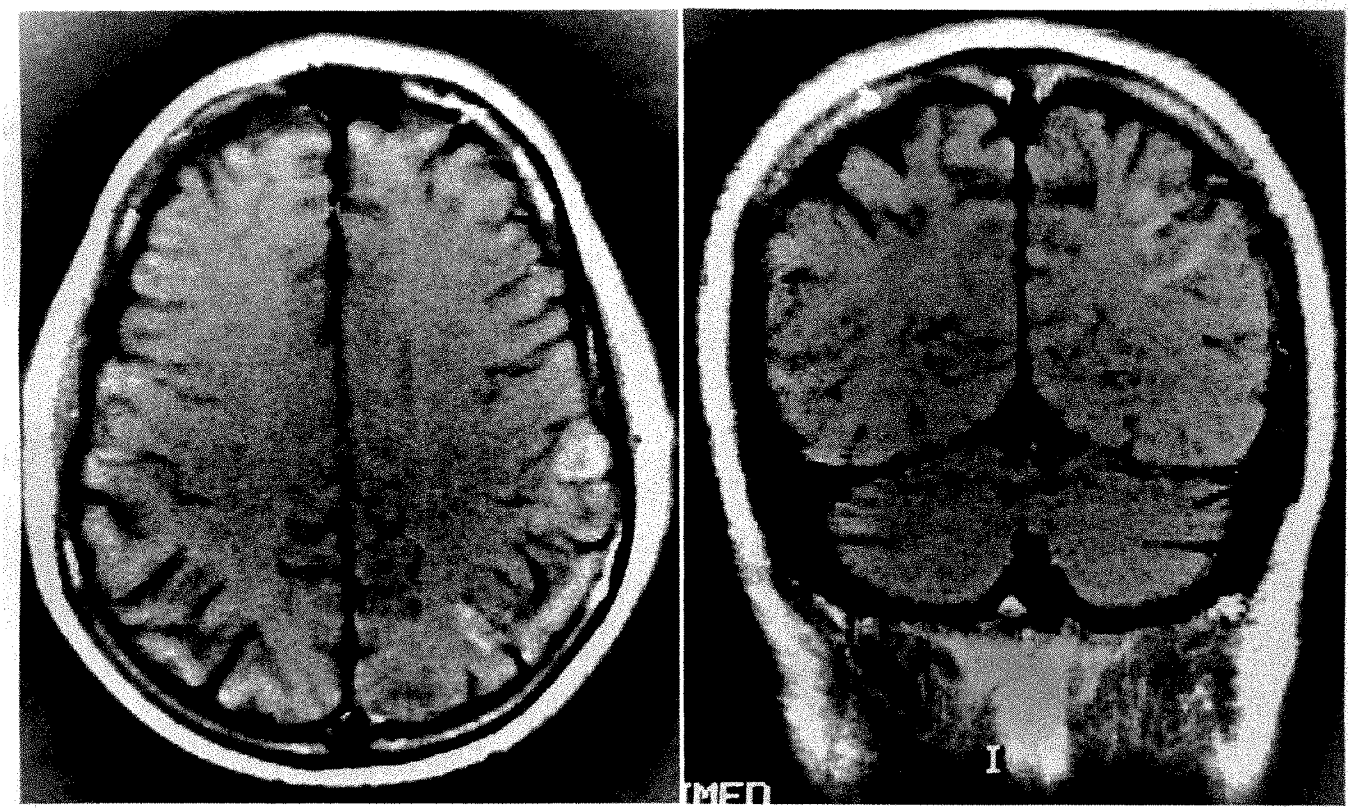

Fig 1.—Patient 1. Magnetic resonance T_1-weighted image after gadolinium injection. Transverse (left) and coronal (right) views show a postcentral infarct extending more caudally within the parietal lobe, involving mainly the cerebral cortex, with little white matter damage. The coronal section (right) shows involvement of the parietal operculum, with damage surrounding the sylvian fissure.

visual acuity, visual fields, and pupil and eye movements were normal. Facial sensation was preserved, with symmetrical corneal reflex. A slight lower facial paresis was present on the right. Tactile, temperature, and pain sensation were normal in the face and mouth. There was no dysphagia and the palate moved symmetrically. The gag reflex was normal. The tongue protruded in the midline. Tendon reflexes were normal and symmetrical. In the limbs, motor strength and tonus were symmetrical and normal. There were elevation and abduction of the left arm, with flexion of the fingers. Fine movements of the fingers (piano playing) were decreased on the left. There was no dysdiadochokinesia or limb dysmetria.

Touch, pain, temperature, and vibration sensation were normal in the four limbs and trunk. Position sensation, stereognosis, and graphesthesia were nearly abolished in the left hand. Sensation was not decreased in the lower limbs, but the patient showed extinction of the left stimulus on simultaneous tactile stimulation of the lower limbs. The results of neuropsychological examination using a standard battery of tests[5] were normal.

The findings of the general examination were normal except for a right carotid bruit. The patient's blood pressure was 219/115 mm Hg. The results of standard blood tests and urinalysis were normal except for a slight anemia (hemoglobin, 126 g/L), an increased cholesterol level (6.2 mmol/L), and slight hyperglycemia (glucose, 6 mmol/L). The electrocardiogram was normal. Doppler ultrasounds and angiography showed a 90% stenosis of the right internal carotid artery. Computed tomography of the brain showed the old right frontal infarct and a recent right postcentral infarct at the level of the parietal operculum (Fig 2).

COMMENT

Both our patients developed cheiro-oral sensory dysfunction in relation to infarct involving the contralateral parietal opercular region. *Cheiro-oral* is a word with Greek-Latin origin, which describes subjective or objective sensory involvement in the peribuccal region and distal part of the upper extremities, mainly the hands and fingers.[6] First described by Sittig[7] in 1914, cheiro-oral sensory involvement, or cheiro-oral syndrome, was thought to be highly suggestive of a cortical lesion in the contralateral hemisphere and corresponded well to the sensory homunculus topography in the cerebral cortex.[6] This assumption was mainly based on the development of paroxysmal cheiro-oral paresthesias, which were likely to be epilectic in patients with tumor or trauma. On the other hand, the role of thalamic involvement was subsequently emphasized in the development of cheiro-oral syndrome,[6] and, in the literature, cheiro-oral syndrome resulting from supratentorial stroke has been reported only in thalamic infarction[8-11] or hemorrhage.[11,12]

The first clinicopathologic study of cheiro-oral syndrome was carried out in 1917 by Schuster,[13] who described a 50-year-old man who experienced paroxysmal tingling in his hand, fingers, and upper lip on the left side, with a slight decrease in position sensation on that side. At autopsy, an "endothelioma" (meningioma) was compressing the lower part of the postcentral gyrus and anterior part of the supramarginal gyrus on the right side; the brain parenchyma itself was not damaged. Seven clinicopathological studies were subsequently published, one involving another patient with a large parietal meningioma,[14] two patients with multiple tuberculomas in the cerebral hemispheres,[15,16] one patient with surgical lesion of the spinothalamic pathways in the midbrain,[17] and three patients with lateral thalamic infarct limited to the ventral posterior nucleus.[8-11] In a review of the literature on cheiro-oral syndrome up to 1965, Haguenau[6] could not find a

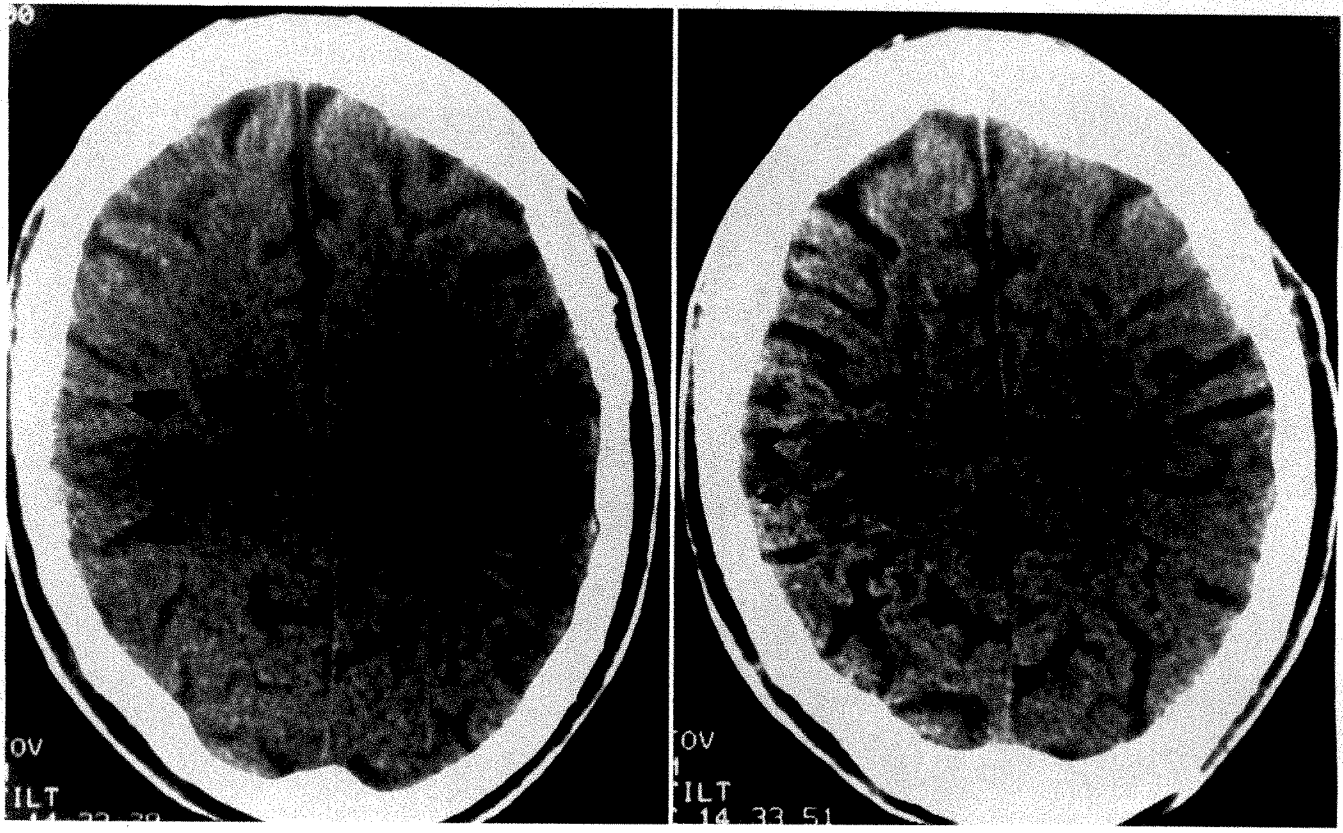

Fig 2.—Patient 2. Computed tomographic scans show a right postcentral infarct (arrows) extending into the underlying white matter.

single case of cortical stroke, and he emphasized thalamic involvement. To our knowledge, no patient has been described with cheiro-oral syndrome and stroke involving the cerebral cortex or underlying white matter on computed tomography or magnetic resonance imaging. Apart from thalamic infarction, cheiro-oral syndrome has been associated with pontine infarct,[11] hemorrhage,[18-21] cavernous angioma,[22] and midbrain hemorrhage[23] on computed tomographic and magnetic resonance imaging scans.

Sensory involvement in our patients was purely subjective in the face, but severe hypoesthesia was present in the hands, without any pseudoradicular distribution. This sensory deficit was "cortical" in type, as position sense, stereognosis, and graphesthesia were particularly severely involved (Verger-Dejerine cortical hypesthesia[24,25]). Pain and temperature sensation were involved in the first patient, but spared in the second patient. Vibration sensation was the least affected sensory modality in both patients. Involvement of the postcentral gyrus in the parietal operculum (somatosensory area I) may explain decreased position and discriminative touch sensation, while involvement of the more caudal portion of the parietal operculum and insula (somatosensory area II) may explain decreased pain and temperature sensation (Dejerine-Mouzon hypoesthesia[26]) by damage to the thalamocortical pathways and to the projection area for nocicepsis.[27-29] Disturbed recognition (eg, stereognosis and pain perception) probably relates to more posterior involvement in the lower parietal region.[28] In fact, dissociated sensory disturbance involving proprioception, stereognosis, and graphesthesia may not be specific for cortical damage, as it has also been reported in pure sensory stroke secondary to thalamic infarction.[29]

Another syndrome with hemisensory disturbance has been reported in patients with left anterior parietal artery territory infarction, associating conduction aphasia, mild motor impairment, and marked faciobrachiocrural hypoesthesia mainly involving the elementary modalities of sensation (ie, touch, position, pain, and temperature).[30-35] In the single autopsied case, the infarct involved the postcentral gyrus P_1 and the anterior part of P_2, but it also extended very deeply into the white matter down to the posterior limb of the internal capsule.[30] A pseudothalamic pain syndrome has also been reported in more posterior involvement of the parietal white matter.[36] Involvement limited to the lower part of the postcentral gyrus, posterior parietal operculum, and underlying white matter in our patients may correspond to infarction in the territory of branches from both the anterior parietal artery and the middle and posterior temporal arteries, without more extensive damage to the anterior parietal artery territory (Fig 3). This type of partial superficial middle cerebral artery branch territory infarct seems rather uncommon, as

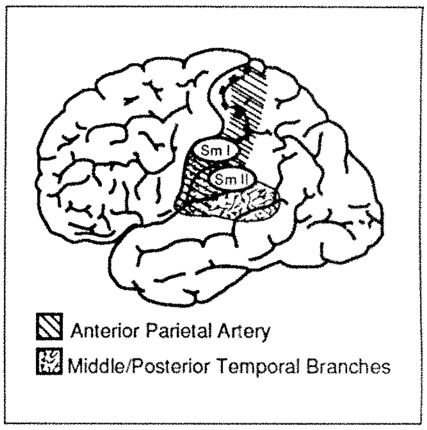
Sm I
Sm II
▨ Anterior Parietal Artery
▩ Middle/Posterior Temporal Branches

Fig 3.—Lateral view of cerebral hemisphere showing somatosensory areas I (Sm I) and II (Sm II) and arterial supply.

suggested by the absence of previous reports of cheiro-oral syndrome resulting from hemisphere stroke. This rarity is difficult to explain, but may be related to the vascular anatomy of the posterior opercular region, which has a double vascular supply through branches from the temporal arteries and anterior parietal artery.[37-41]

Our findings highlight the nonspecificity of cheiro-oral sensory disturbance in acute stroke. They also provide evidence for partial middle cerebral artery territory infarction limited to the posterior opercular region.

References

1. Alajouanine T, Boudin G, Pertuiset B, Pépin B. Le syndrome unilatéral de l'opercule rolandique avec atteinte contralatérale du territoire des V, VII, IX, X, XI et XIIe nerfs crâniens. *Rev Neurol.* 1959;101:168-171.

2. Schott B, Boulliat G, Cotte L, Vauterin C. Le syndrome operculaire bilatéral et unilatéral. *Lyon Med.* 1961;365-377.

3. Bruyn GW, Gathier JC. The operculum syndrome. In: Vinken PJ, Bruyn GW, eds. *Handbook of Clinical Neurology.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1972:776-783.

4. Mao CC, Coull BM, Golper LAC, Rau MT. Anterior operculum syndrome. *Neurology.* 1989;39:1169-1172.

5. Assal G. *Batterie des examens neuropsychologiques du CHUV.* Lausanne, Switzerland: Centre Hospitalier Universitaire Vaudois; 1985.

6. Haguenau MD. *Contribution à l'étude des syndromes sensitifs cheiro-oraux.* Paris, France: R Foulon et Cie; 1965. Thesis.

7. Sittig O. Klinische Beiträge zur Lehre von den sensiblen Kindenzentren. *Prager Med Wochenschr.* 1914;39:548-550.

8. Garcin R, Lapresle J. Syndrome sensitif de type thalamique et à topographie cheiro-orale par lésion localisée au thalamus. *Rev Neurol.* 1954; 90:124-129.

9. Garcin R, Lapresle J. Deuxième observation personnelle du syndrome sensitif de type thalamique à topographie cheiro-orale par lésion localisée du thalamus. *Rev Neurol.* 1960;103:474-481.

10. Fisher CM. Pure sensory stroke involving face, arm and leg. *Neurology.* 1965;15:76-80.

11. Kawakami Y, Chikama M, Tanimoto T, Shimamura Y. Radiological studies of the cheiro-oral syndrome. *J Neurol.* 1989;236:177-181.

12. Awada A. Fourmillements cheiro-faciaux isolés par hématome thalamique. *Rev Neurol.* 1989;145:861-862.

13. Schuster P. Beiträge zur Lehre von den sensiblen Zentren der Grosshirnrinde. *Neurol Zentralbl.* 1917;36:331-336.

14. Guillain G, Alajouanine T, Darquier J. Considérations diagnostiques à propos d'un cas d'endothéliome de la région rolandique basse: la valeur sémiologique de l'abolition du réflexe cornéen dans les syndromes corticaux. *C R Soc Biol (Paris).* 1931;107:1274-1276.

15. Strauss H. Über Sensibilitätsstörungen an Hand und Gesicht, Geschmacksstörungen und ihre lokalilisatorische Bedeutung. *Monatsschr Psychiat Neurol.* 1925;58:265-276.

16. Roger H, Alliez J, Paillas J, Jouve A. Migraines accompagnées de paresthésies cheiro-orales symptomatiques d'un début de méningite tuberculeuse de l'adulte. *Gaz Hop.* 1936;109:111-113.

17. Mark VH, Ervin FR, Yakovlev PI. The treatment of pain by stereotaxic methods. *Conf Neurol (Basel).* 1962;22:238-245.

18. Araga S, Fukada M, Kagimoto H, Takahashi K. Pure sensory stroke due to pontine haemorrhage. *J Neurol.* 1987;235:116-117.

19. Iwasaki Y, Kinoshita M, Ikeda K, Shiojima T. Pure sensory stroke and cheiro-oral syndrome. *J Neurol.* 1989;236:186-187.

20. Yasuda Y, Akiguchi I, Ishikawa M, Kameyama M. Bilateral cheiro-oral syndrome following pontine haemorrhage. *J Neurol.* 1988;235:489-490.

21. Matsumoto S, Kaku S, Yamasaki M, Imai T, Nabatawe H, Kameyama M. Cheiro-oral syndrome with bilateral oral involvement: a study of pontine lesions by high-resolution MRI. *J Neurol Neurosurg Psychiatry.* 1989;52:792-794.

22. Ten Holter J, Tijssen C. Cheiro-oral syndrome: does it have a specific localizing value? *Eur Neurol.* 1988;28:326-330.

23. Ono S, Inoue K. Cheiro-oral syndrome following midbrain haemorrhage. *J Neurol.* 1985; 232:304-306.

24. Verger H. Sur les troubles de la sensibilité générale consécutifs aux lésions des hémisphères cérébraux chez l'homme. *Arch Gen Med.* November-December 1900:513, 662

25. Dejerine J. *Sémiologie des affections du système nerveux.* New York, NY: Masson Publishers USA Inc; 1914;2:915.

26. Dejerine J, Mouzon J. Un nouveau type de syndrome sensitif cortical observé dans un cas de monoplégie corticale dissociée. *Rev Neurol.* 1915;2:1265-1273.

27. Biemond A. The conduction of pain above the level of the thalamus opticus. *Arch Neurol Psychiatry.* 1956;75:231-244.

28. Brodal A. *Neurological Anatomy in Relation to Clinical Medicine.* New York, NY: Oxford University Press Inc; 1981.

29. Carpenter MB. *Human Neuroanatomy.* Baltimore, Md: Williams & Wilkins; 1976.

30. Pause M, Kunesch E, Binkofski F, Freund HJ. Sensorimotor disturbances in patients with lesions of the parietal cortex. *Brain.* 1989; 112:1599-1625.

31. Sacco RL, Bello JA, Traub R, Brust JCM. Selective proprioceptive loss from a thalamic lacunar stroke. *Stroke.* 1987;18:1160-1163.

32. Foix C, Chavany JA, Lévy M. Syndrome pseudo-thalamique d'origine pariétale: lésion de l'artère du sillon interpariétal (Pa P_1 P_2 antérieures, petit territoire insulo-capsulaire). *Rev Neurol.* 1927;35:68-76.

33. Lhermitte F, Desi M, Signoret JL, Deloche G. Aphasie kinesthésique associée à un syndrome pseudothalamique. *Rev Neurol.* 1980;136:675-688.

34. Bogousslavsky J, Assal G, Regli F. Aphasie afférente motrice et hémisyndrome sensitif droit: le syndrome de l'artère pariétale antérieure gauche. *Rev Neurol.* 1982;138:649-655.

35. Poncet M, Habib M, Robillard A. Deep left parietal lobe syndrome: conduction aphasia and other neurobehavioral disorders due to a small subcortical lesion. *J Neurol Neurosurg Psychiatry.* 1987;50:709-713.

36. Hyman BT, Tranel D. Hemianesthesia and aphasia: an anatomical and behavioral study. *Arch Neurol.* 1989;46:816-819.

37. Bogousslavsky J, Van Melle G, Regli F. Middle cerebral artery pial territory infarcts: a study of the Lausanne Stroke Registry. *Ann Neurol.* 1989;25:555-560.

38. Schmahmann JD. Parietal pseudothalamic pain syndrome. *Neurology.* 1989;39(suppl 1):358.

39. Foix C, Lévy M. Les ramollissements sylviens: syndromes des lésions en foyer du territoire de l'artère sylvienne et de ses branches. *Rev Neurol.* 1927;2:1-51.

40. Salamon G, Huang YP. *Radiologic Anatomy of the Brain.* New York, NY: Springer-Verlag NY Inc; 1976.

41. Damasio H. A computed tomographic guide to the identification of cerebral vascular territories. *Arch Neurol.* 1983;40:138-142.

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FAX: (615) 395-4764

Professional Opportunities

SOUTHEAST COAST — The Neuroscience Center of a 190-bed regional medical center is seeking a BC/BE neurologist to join in close association with their existing neurosurgeons. Exceptional medical facilities and neurological services including EEG/EMG, EP, CT, MRI. Excellent income guarantee plus benefits — large drawing area provides for outstanding potential. Located ninety minutes from one of this country's premiere seaside resorts, this dynamic community offers a quality lifestyle. Call Mark Prosperi at (800) 776-5776 for more details or send CV to: Cejka & Co., 1034 South Brentwood Boulevard, St. Louis, MO 63117.

SOUTHEAST COAST — Pediatric Neurologist: Excellent quality of life available in Savannah-Hilton Head Area, site of the 1996 Olympic Games sailing events. Outstanding recreational opportunities, nation's largest urban Historic District, and superb symphony are among the attractions of living here. A well-trained, personable neurologist with special competence in child neurology is needed for a busy practice, currently consisting of two adult neurologists and one neurologist doing adult and child neurology, all with strong academic backgrounds. CT, EEG, EMG and physical therapy are available in-office with large hospital practice available in three hospitals, including a major regional teaching hospital, affiliated with the Medical College of Georgia. First year guarantee is $80,000 plus bonus, leading to full partnership after two years. Earnings potential, availability of strong multi-specialty support, and opportunities for teaching are extraordinary. If interested contact: Randy Wellman, Office Manager, Savannah Neurological Associates, PC, P.O. Box 23059, Savannah, GA 31403. (912) 354-8151.

ADULT NEUROLOGIST to associate with two separate, busy solo neurologists. Practices are referral based, with two separate offices and three voluntary hospitals. Successful candidate would be expected to develop a separate solo, but collaborative practice. Established physicians would expect to provide substantial support for beginning physician. Opportunity would provide for cross coverage and joint venturing of facilities. Successful candidate should have excellent clinical skills. The medical community has excellent neurophysiology, neuroradiology, and neurosurgery. Located in a medium size city with both excellent living conditions and an extremely solid economic base. Please contact: Jeffrey A. Ribner, MD, 503 Plaza Drive, Vestal, NY 13850. (607) 729-1521 or Robert R. Taylor, Jr., MD, 269 Riverside Drive, Johnson City, NY 13790. (607) 798-7143.

SEEKING ENERGETIC BE/BC NEUROLOGIST to join three adults and one child neurologist. Prefer someone with interest in general neurology and special interest and training in any of the following areas: sleep medicine, neurophysiology testing, neuro-rehabilitation, pain, or neuro-intensive care. Excellent medical community with all of the supportive consultants and technology. Send CV to: Neurological Associates of Grand Rapids, PC, 2855 Michigan Street, Northeast, Grand Rapids, MI 49506.

NEUROLOGIST — BC/BE, full- or part-time, for exanding San Francisco Bay area. Private practice with emphasis on clinical occupational neurology and med-legal evaluations. Expertise in EMG, EEG and EP desired. Excellent reputation, referral base, facilities and support staff. Unique income opportunity. Submit CV and letter stating professional goals, and availability to: Personnel, 2040 Polk Street, Box 337, San Francisco, CA 94109.

NEUROLOGIST TO DIRECT Movement Disorders Program — The Cleveland Clnic Department of Neurology is seeking a BE/BC neurologist to direct and develop a major Movement Disorders Program. Fellowship training in movement disorders is highly desirable, as is experience with clinical research trials especially related to Parkinson's disease. This is an outstanding opportunity to join a premier clinical neurology group with a strong commitment to education and research. Interested individuals should send CV and three references to: Anthony J. Furlan, MD, Head, Section of Adult Neurology or Hans Luders, MD, PhD, Chairman, Department of Neurology, The Cleveland Clinic Foundation, One Clinic Center, Cleveland, OH 44195. The Cleveland Clinic Foundation is an equal opportunity/affirmative action employer.

Professional Opportunities

FOOTHILLS OF MOUNTAINS where Tennessee, North Carolina and Virginia meet. Busy general neurology practice with opportunity to develop subspecialty interest in epilepsy, sleep, pediatrics, trauma or rehab. Plentiful EMGs and EEGs. Appointment at state university medical school. Community boasts award winning schools, affluent patient base, boating, snow-skiing, camping and the arts. Call Daine Safner at: (800) 765-3055. Or send CV to: 222 South Central, Suite 700, St. Louis, MO 63105.

NEUROLOGIST — Beautiful Durango, Colorado is recruiting a BC/BE neurologist. Mercy Medical Center is an extremely progressive and active 100-bed facility and is doing well financially and growing — primarily due to an excellent staff of 90 physicians and a decent economy. Durango is located in southwestern Colorado, with an abundance of outdoor recreation (skiing, fishing, hunting, bicycling) excellent restaurants, an excellent local 4-year college, great weather and excellent schools! For more information about this excellent practice opportunity, mail CV or call: Bob Conrad, Vice President, Mercy Medical Center, 375 East Park Avenue, Durango, CO 81301. (303) 247-3804.

The Division of Movement Disorders in the Department of Neurology of Henry Ford Hospital is seeking a second neurologist to join the Gossett Parkinson's Disease Center.

The candidate should have fellowship training in movement disorders. The position will include half-time for research activities. The department is large, committed to academic excellence, and offers excellent research opportunities in NMR spectroscopy, pharmacology, epidemiology, neuropsychology and basic neurobiology. Candidates should be capable of developing a research program, partly collaborating with others in the center. Competitive salary and benefits are offered, commensurate with experience.

Send CV and two references to:

Jay M. Gorell, MD, Director
Division of Movement Disorders and
Gossett Parkinson's Disease Center
Department of Neurology
Henry Ford Hospital
2799 West Grand Boulevard
Detroit, Michigan 48202.

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EXCELLENT OPPORTUNITY for BC/BE neurologist to join 80-physician comprehensive, multi-specialty group in San Francisco Bay Area. Large, varied referral base from Pediatrics, IM, FP, and Surgery. EMG/NCV, EEG, Evoked Response Testing, CT, MRI, Radiology support all available on site. Opportunity to interface with specialists of all types including neurosurgeons. Major university teaching affiliation encouraged and possible. Close proximity to 400-bed full service, modern hospital serving population of 300,000. Comeptitive guaranteed salary with bonus productivity plan for initial 18 months leading to partnership track. Extensive benefit package including housing incentives. Unique cultural, recrational and educational opportunities. Send CV to: Gary D. Zweig, MD, Recruitment Chairman, Sunnyvale Medical Clinic, P.O. Box 3496, Sunnyvale, CA 94088-3496.

BC/BE NEUROLOGIST — Exceptional opportunity to establish a practice in northwest Denver suburb. No investment required. Strong referral base. Opportunity to affiliate with two busy neurologists with office located adjacent to beautiful 400-bed hospital with state-of-the-art technology. Excellent opportunity for subspecialty trained with a strong interest in the clinical care of patients. Send CV to: Box #819, c/o AON.

PLEASE NOTE—Address replies to box number ads as follows: Box number ______, c/o AON, P.O. Box 1510, Clearwater, FL 34617.

Professional Opportunities

NEUROLOGIST — BOARD-CERTIFIED or -eligible neurologist with California license needed to join a prestigious Worker's Compensation clinic for patient evaluation and follow-up and EMG/NCS testing. For further information contact Christine Benson at: (213) 277-2929. Or send CV to: 1125 South Beverly Drive, #601, Los Angeles, CA 90035.

ROCKY MOUNTAINS

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For additional information about this excellent opportunity, call Greg Peterson at: (800) 669-4804 or (913) 599-4804.

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Shawnee Mission, KS 66215

NEUROLOGIST: BC/BE neurologist to replace retiring partner in established four-person department associated with 106-physician multi-specialty clinic located in beautiful northwest Arkansas. Holt-Krock Clinic is the 33rd largest freestanding clinic in the nation, serving a patient base of 400,000 in Arkansas and Oklahoma. Full range of electrical studies offered with EEG, EMG, evoked response, and cervical vascular ultrasound procedures. We offer a guaranteed salary with full partnership in 2 to 2½ years, plus excellent fringe benefits. 680-bed hospital and new rehab hospital two blocks from main clinic. For details regarding this opportunity, send letter and CV to: Mrs. Josephine Decker, Associate Administrator, Holt-Krock Clinic, 1500 Dodson Avenue, Fort Smith, AR 72901. (501) 782-2071.

EXPANDING, DYNAMIC ADULT neurology practice — BC/BE neurologist to join rapidly growing office and multi-hospital practice in New Jersey — 15 minutes from Manhattan. Candidate must be energetic and personable. EMG, EEG experience preferred. Send CV to: Joseph Sobelman, MD, 834 Avenue C, Bayonne, NJ 07002.

Faculty Positions

LOYOLA UNIVERSITY Chicago Stritch School of Medicine, Department of Neurology invites applications for two positions at the Assistant Professor level. Applicants should be board-eligible or -certified in neurology and have subspecialty expertise in either epilepsy, movement disorders, cerebrovascular diseases, behavioral or geriatric neurology. Preference will be given to candidates with clinical research interests. Send CV to: Gastone Celesia, MD, Chairman, Neurology Department, Loyola University Chicago, 2160 South First Avenue, Chicago, IL 60153. Loyola University Chicago is an equal opportunity/affirmative action employer.

NEUROLOGIST BC/BE: The Texas College of Osteopathic Medicine is recruiting an academically oriented neurologist with interest in clinical neurology, teaching and research. Faculty appointment provides competitive salary with excellent fringe benefits. Please send curriculum vitae and letter of inquiry to William E. McIntosh, DO, Associate Professor of Medicine/Neurology, Texas College of Osteopathic Medicine, 3500 Camp Bowie Boulevard, Fort Worth, TX 76107. TCOM is an affirmative action/equal opportunity employer.

FULL-TIME TENURE-TRACK faculty opportunities available for BC/BE neurologists with dementia, EMG/neuromuscular diseases and cerebrovascular disease expertise. Successful applicants will be provided laboratory space and support in a dynamic growing department, take an active role in the Creighton-Nebraska neurology training program and be afforded ample research and clinical collaborative opportunities for career advancement. Creighton is an established university and medical center with expanding and diverse facilities, including a new PET Center. Send inquiries to: John M. Bertoni, MD, PhD, Professor and Chairman, Department of Neurology, 601 North 30th Street, Suite 2342, Omaha, NE 68131. EOE.

Faculty Positions

THE UNIVERSITY OF Mississippi Medical Center Department of Neurology invites applications for position of Assistant Professor from board-certified individuals with strong research, clinical and teaching skills. Persons with expertise in neuro-oncology, vascular disease, and epilepsy are especially being sought. Please submit a letter of intent, curriculum vitae, and letters of recommendation from three physicians to: Dr. James J. Corbett, Chairman, Department of Neurology, The University of Mississippi Medical Center, Jackson, MS 39216-4505. The University of Mississippi Medical Center is an equal opportunity employer. M/F/H/V.

ACADEMIC NEUROLOGIST: University Colorado School Medicine, Denver. Full-time faculty position based at Denver General Hospital. Responsibilities include inpatient attending, outpatient clinics, training neurology residents and teaching medical students clinical neurology. Clinical research and EMG experience desirable, but not required. CV: Donald Gilden, MD, Chairman, Department Neurology, 4200 East 9th Avenue, Denver, CO 80262. AA/EOE.

Residencies

PGY-III — University of South Alabama Medical Center invites applications for a PGY-III position in Neurology beginning July 1, 1991. Reply to: Paul Dyken, MD, Professor and Chairman, Department of Neurology, 2451 Fillingim Street, Mobile, AL 36617. Telephone: (205) 471-5801.

ADULT NEUROLOGY RESIDENCY PGY-IV position available at the University of Colorado School of Medicine for July, 1991. Contact: James P. Kelly, MA, MD, Director of Resident Selection, Department of Neurology, UCHSC B-183, 4200 East Ninth Avenue, Denver, CO 80262. (303) 270-8760.

CHILD NEUROLOGY RESIDENCY. The Department of Neurology at the Medical College of Wisconsin has a first year position available for July 1, 1992, in a fully accredited three-year training program at the new Children's Hospital of Wisconsin. There are five full-time pediatric neurologists conducting a strong general clinical neurology program with programs of special emphasis in both clinical and basic science in oncology, epilepsy, neurobehavior, and neuromuscular disorders. Candidates should have two years of pediatric training in an ACGME-accredited program. Contact: Richard J. Konkol, MD, PhD, Chief, Section of Pediatric Neurology, 8701 Watertown Plank Road, Milwaukee, WI 53226. Telephone (414) 266-4090, or Eric Maas, MD, Neurology Residency Director, Froedtert Memorial Lutheran Hospital, 9200 West Wisconsin Avenue, Milwaukee, WI 53226.

Miscellaneous

WRITE BRIEF REVIEWS on topics in neurology for $500-$1,000. Respond with CV to: Dr. S. Demeter, Arbor Publishing Corp., 333 Metro Park, Suite N-208, Rochester, NY 14623.

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Columbia, MD 21044

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1985 NIHON KOHDEN Neuropack 8 Evoked Potential Machine-VEP, BAEP, SSEP; with color monitor and plotter. Excellent condition: $15,000. (703) 885-6000.

Positions Wanted

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Directors Wanted

DIRECTOR, CLINICAL EEG/EP laboratory with an appointment in Department of Neurology, Harvard Medical School, is sought by the Neurology Division, Brigham and Women's Hospital, Boston. The successful candidate will direct the clinical, investigative and teaching aspects of the EEG and EP laboratory. Applicants should be board-certified neurologists with demonstrated facility in neurophysiology. Clinical skill and laboratory expertise are equally important aspects of the position. Please send inquiries and CV to: Martin A. Samuels, MD, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Brigham and Women's Hospital and Harvard Medical School are equal opportunity employers.

DIRECTOR, Neurology-Neurosurgery Intensive Care Unit with an appointment in Department of Neurology, Harvard Medical School, is sought by the Neurology Division, Brigham and Women's Hospital, Boston. The successful candidate will direct the clinical, investigative and teaching aspects of Neuro-ICU. Applicants should be board-certified in Neurology and Internal Medicine with demonstrated facility in organizing and operating a Neuro-ICU. Clinical skill and clinical research facility are equally important aspects of the position. Please send inquiries and CV to: Martin A. Samuels, MD, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115. Brigham and Women's Hospital and Harvard Medical School are equal opportunity employers.

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Synergen, Inc., a growing biotechnology company in Boulder, Colorado, seeks experienced Associate Clinical Directors for the clinical evaluation of several innovative recombinant DNA protein therapies for wound healing, inflammation, sepsis, pulmonary and neurological diseases. As part of the new clinical team, these two new positions will work with the Medical Director to plan clinical research projects and to design, monitor, evaluate and report clinical trials.

Requirements include M.D. degree with specialty training in neurology for one position. For the other position requirements include M.D. degree with specialty training in pediatrics or internal medicine with subspecialty training in pulmonology. Approximately 2-3 years' experience in pharmaceutical industry positions that have provided a thorough background in the design and execution of clinical studies (Phases I through III) required. The successful candidates should have the ability to develop, execute and manage a fully integrated clinical trial program.

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Before prescribing, please see full prescribing information. A Brief Summary follows.

INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states
referred to as "delirium," "psychosis," or "encephalopathy," o
dysfunction. Accordingly, at the first sign of acute toxicity, plasma
reduction of phenytoin therapy is indicated if plasma levels are e
termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be
adhering strictly to the prescribed dosage regimen, and of inform
condition in which it is not possible to take the drug orally as p

Patients should also be cautioned on the use of other drugs or
seeking the physician's advice.

Patients should be instructed to call their physician if skin ras

The importance of good dental hygiene should be stres
development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may b
dosage adjustments.

Drug Interactions: There are many drugs which may increase
which phenytoin may affect. Serum level determinations for p
when possible drug interactions are suspected. The most comm
are listed below: 1. Drugs which may increase phenytoin seru
intake, amiodarone, chloramphenicol, chlordiazepoxide, diaz
estrogens, H_2-antagonists, halothane, isoniazid, methyl
phenylbutazone, salicylates, succinimides, sulfonamides, tolb

2. Drugs which may decrease phenytoin levels include: carbam
reserpine, and sucralfate. Moban® brand of molindone hydroc
which interfere with the absorption of phenytoin. Ingestion ti
preparations containing calcium should be staggered in patients
to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin seru
sodium valproate, and valproic acid. Similarly, the effect of pheny
acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressa
susceptible patients and phenytoin dosage may need to be adj

5. Drugs whose effi
include: corticosteroi
digitoxin, doxycycline,
contraceptives, quini
vitamin D.

Drug/Laboratory Test
cause decreased seru
(PBI). It may also produ
dexamethasone or met
cause increased serum
phatase, and gamma g

Carcinogenesis: See "
tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for w
phenytoin appears to be secreted in low concentrations in hum

ADVERSE REACTIONS: Central Nervous System: The most comm
with phenytoin therapy are referable to this system and are usual
nystagmus, ataxia, slurred speech, decreased coordination and
insomnia, transient nervousness, motor twitchings, and headaches
have also been rare reports of phenytoin induced dyskinesias, incl
and asterixis, similar to those induced by phenothiazine and other

A predominantly sensory peripheral polyneuropathy has been
long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxi

Integumentary System: Dermatological manifestations sometim
included scarlatiniform or morbilliform rashes. A morbilliform r
common; other types of dermatitis are seen more rarely. Other m
be fatal have included bullous, exfoliative or purpuric dermatitis, l
Johnson syndrome, and toxic epidermal necrolysis (see Precau

Hemopoietic System: Hemopoietic complications, some fatal, h
in association with administration of phenytoin. These have inclu
penia, granulocytopenia, agranulocytosis, and pancytopenia wit
pression. While macrocytosis and megaloblastic anemia have occ
respond to folic acid therapy. Lymphadenopathy including benign
dolymphoma, lymphoma, and Hodgkin's Disease have been rep

Connective Tissue System: Coarsening of the facial features, en
hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, b
such as arthralgias, eosinophilia, fever, liver dysfunction, lympha
lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The leth
to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, a
tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiti
comatose and hypotensive. Death is due to respiratory and circu

There are marked variations among individuals with respect to
toxicity may occur. Nystagmus, on lateral gaze, usually appear
mcg/mL, dysarthria and lethargy appear when the plasma concen
as high a concentration as 50 mcg/mL has been reported without
as 25 times the therapeutic dose has been taken to result in a s
mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known ant

The adequacy of the respiratory and circulatory systems shou
appropriate supportive measures employed. Hemodialysis can b
is not completely bound to plasma proteins. Total exchange tran
treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants,
borne in mind.

Caution – Federal law prohibits dispensing without prescription.

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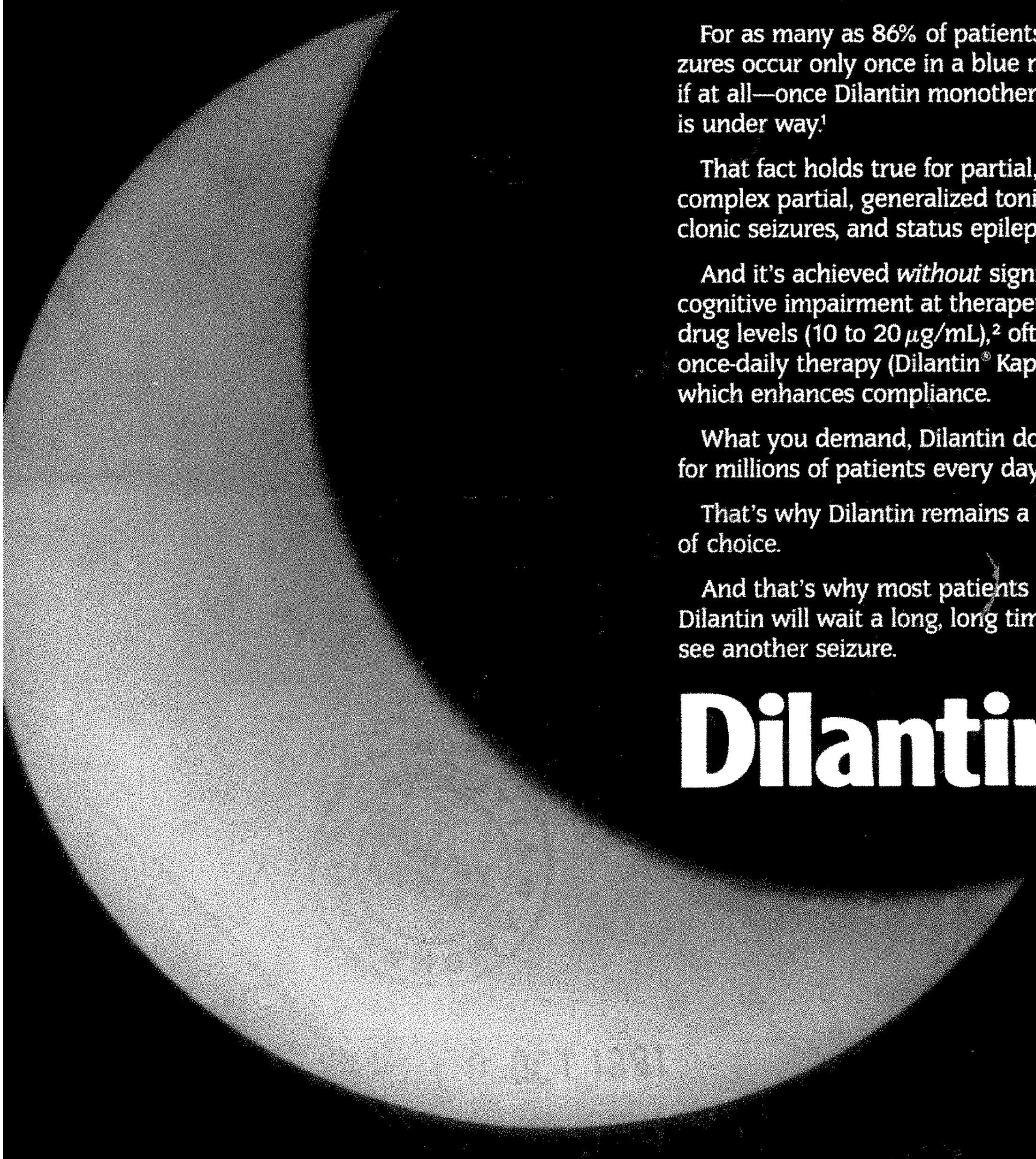

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nce in a blue moon" describes the phenomenon in which he moon appears as a brilliant blue. Seen worldwide following he volcanic eruption of Krakatoa in 1883, the blue moon occurs nly when atmospheric cloud droplets, each less than 5 μm in iameter, form in abundance—an exceedingly rare event.[3]

References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976; 31:292-296.

Please see adjacent page for brief summary of prescribing information.

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121

ARCHIVES OF Neurology

SEPTEMBER 1991

The Epidemiology of Parkinson's Disease: A Case-Control Study of Young-Onset and Old-Onset Patients
M. Stern, E. Dulaney, S. B. Gruber, L. Golbe, M. Bergen, H. Hurtig, S. Gollomp, P. Stolley

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Clinical and Genetic Analysis of Progressive Dystonia With Diurnal Variation
J. K. Fink, P. D. Ravin, M. Filling-Katz, C. E. Argoff, M. Hallett

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Abnormalities of Cutaneous Blood Flow Regulation in Patients With Reflex Sympathetic Dystrophy as Measured by Laser Doppler Fluxmetry
M. D. Bej, R. J. Schwartzman

Transient Ischemic Attacks With and Without a Relevant Infarct on Computed Tomographic Scans Cannot Be Distinguished Clinically
P. J. Koudstaal, J. van Gijn, J. Lodder, C. W. G. M. Frenken, M. Vermeulen, C. L. Franke, A. Hijdra, C. Bulens, for the Dutch Transient Ischemic Attack Study Group

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Nuclear Hemodynamic Vertebrobasilar Insufficiency: A New Approach With the Xenon Xe 133 Method
P. Trouillas, N. Nighoghossian, B. Philippon

Volume 48, Number 9

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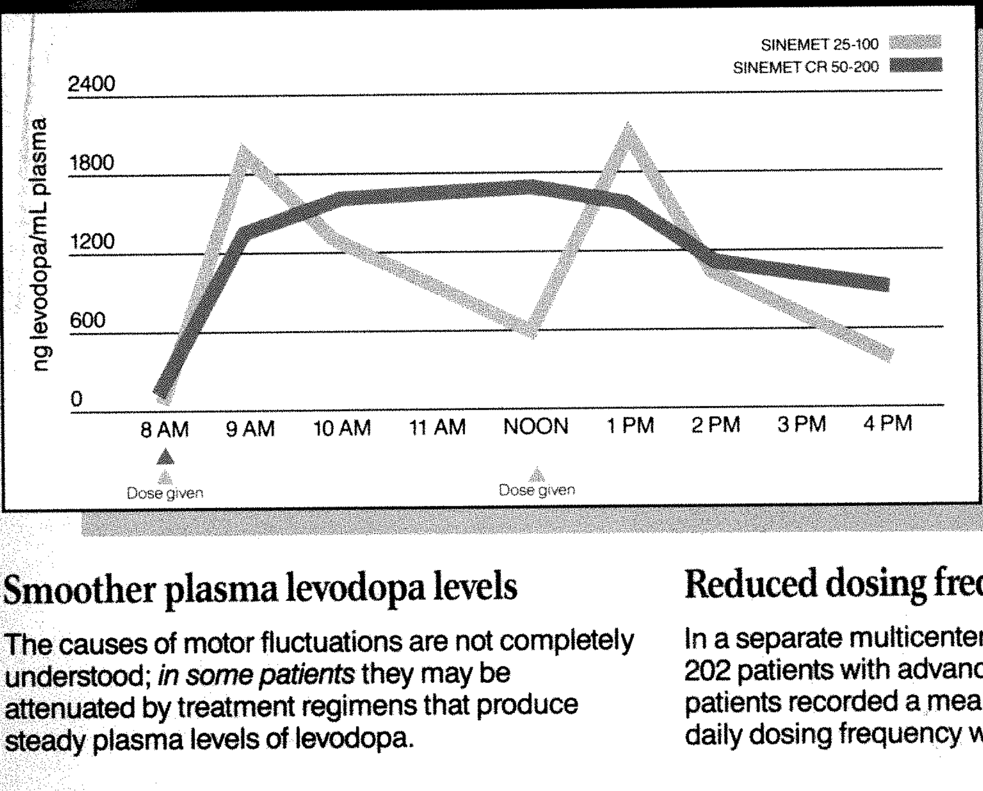

Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)[1]

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

Smoother plasma levodopa levels

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Reduced dosing frequency[2]

In a separate multicenter, double-blind trial of 202 patients with advanced Parkinson's disease, patients recorded a mean reduction of 33% in daily dosing frequency with SINEMET CR.[2]

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*Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

Before prescribing SINEMET CR, please see Full Prescribing Information on the following pages.

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SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

1. Goetz CG, Tanner CM, Shannon KM, et al: Controlled-release carbidopa/levodopa (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuations. *Neurology.* 1988;38:1143-1146.
2. Hutton JT, Morris JL, Bush DF, et al: Multicenter controlled study of Sinemet CR vs Sinemet (25/100) in advanced Parkinson's disease. *Neurology.* 1989;39 (suppl 2): 67-72.

- Significantly greater benefits as rated by patients previously treated with SINEMET® (Carbidopa-Levodopa)‡[2]
- Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.
- Significantly greater clinical improvement in patients with moderate to severe motor fluctuations as rated by physicians**[2]
- In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations while on SINEMET were randomized to therapy with either SINEMET or SINEMET CR: *Adverse experience profile of SINEMET CR did not differ substantially from that of SINEMET.*

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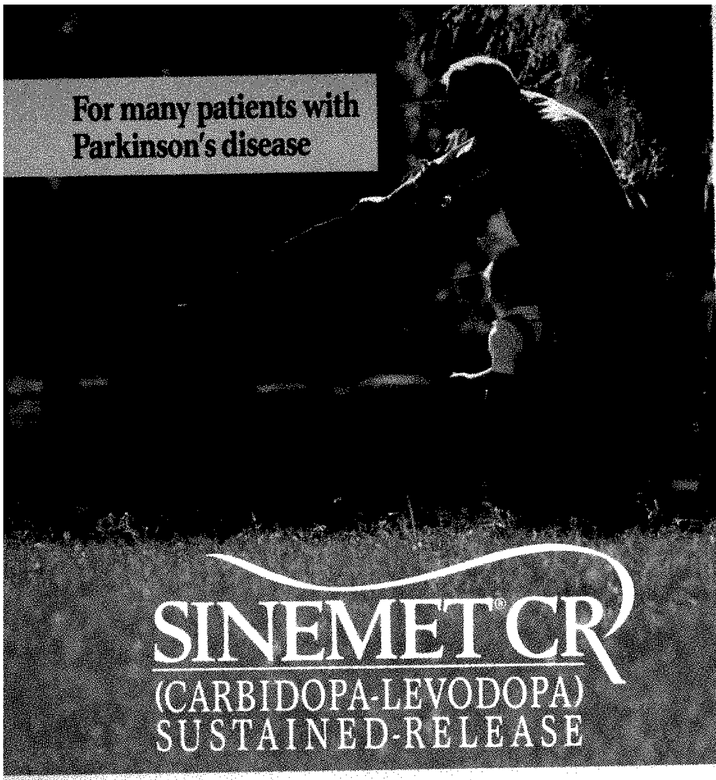
†In clinical trials of patients with moderate to severe motor fluctuations, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

‡Ratings based on patients' subjective assessment of global improvement in clinical fluctuations.

**Physician ratings based on significantly greater overall improvement in patient's clinical condition after eight weeks on SINEMET CR (compared to status at beginning of double-blind phase of same trials).[2]

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. It is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B, (e.g., selegiline HCl). SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma. Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.



Guidelines for Initial Conversion from SINEMET® to SINEMET CR

(Carbidopa-Levodopa)

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION, *Titration.*)*
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen†
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

*The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

†For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* of enclosed Full Prescribing Information.

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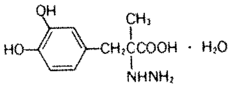
SINEMET® CR (CARBIDOPA-LEVODOPA)

SUSTAINED-RELEASE TABLETS

DESCRIPTION

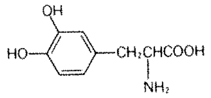
SINEMET* CR (Carbidopa-Levodopa) is a sustained-release combination of carbidopa and levodopa for the treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in water, with a molecular weight of 244.3. It is designated chemically as (−)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propanoic acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \bullet H_2O$ and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound slightly soluble in water, with a molecular weight of 197.2. It is designated chemically as (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formula is $C_9H_{11}NO_4$ and its structural formula is:



SINEMET CR is supplied as sustained-release tablets containing 50 mg of carbidopa and 200 mg of levodopa. Inactive ingredients in SINEMET CR are: D & C Yellow 10, magnesium stearate, iron oxide, and other ingredients.

SINEMET CR is supplied as an oval, scored, biconvex, compressed tablet that is peach colored. The tablet is a polymeric-based drug delivery system which controls the release of carbidopa and levodopa as it slowly erodes.

CLINICAL PHARMACOLOGY

Pharmacodynamics Current evidence indicates that symptoms of Parkinson's disease are related to depletion of dopamine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease apparently because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross the blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whereby levodopa relieves symptoms of Parkinson's disease.

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a small portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levodopa are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, some of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa may be impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not affect the metabolism of levodopa within the central nervous system.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levodopa makes more levodopa available for transport to the brain.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by end-of-dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is characterized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not completely understood, *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

SINEMET CR contains 50 mg of carbidopa and 200 mg of levodopa in a sustained-release dosage form designed to release these ingredients over a 4 to 6 hour period. With SINEMET CR there is less variation in plasma levodopa levels than with SINEMET* (Carbidopa-Levodopa), the conventional formulation. *However, SINEMET CR (Carbidopa-Levodopa, Sustained-Release) is less systemically bioavailable than SINEMET (Carbidopa-Levodopa) and may require increased daily doses to achieve the same level of symptomatic relief as provided by SINEMET (Carbidopa-Levodopa).*

In clinical trials, patients with moderate to severe motor fluctuations *who received SINEMET CR did not experience quantitatively significant reductions* in 'off' time when compared to SINEMET (Carbidopa-Levodopa). However, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET (Carbidopa-Levodopa). In patients without motor fluctuations, SINEMET CR, under controlled conditions, provided the same therapeutic benefit with less frequent dosing when compared to SINEMET (Carbidopa-Levodopa).

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increasing the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

Pharmacokinetics Carbidopa reduces the amount of levodopa required to produce a given response by about 75 percent and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decreases plasma and urinary dopamine and homovanillic acid.

Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following SINEMET CR, the apparent half-life of levodopa may be prolonged because of continuous absorption.

In healthy elderly subjects (56-67 years old) the mean time to peak concentration of levodopa after a single dose of SINEMET CR 50-200 was about 2 hours as compared to 0.5 hours after standard SINEMET (Carbidopa-Levodopa). The maximum concentration of levodopa after a single dose of SINEMET CR was about 35% of the standard SINEMET (Carbidopa-Levodopa) (1151 vs 3256 ng/mL). The extent of availability of levodopa from SINEMET CR was about 70-75% relative to intravenous levodopa or standard SINEMET (Carbidopa-Levodopa) in the elderly. The absolute bioavailability of levodopa from SINEMET CR (relative to I.V.) in young subjects was shown to be only about 44%. The extent of availability and the peak concentrations of levodopa were comparable in the elderly after a single dose and at steady state after t.i.d. administration of SINEMET CR 50-200. In elderly subjects, the average trough levels of levodopa at steady state after the CR tablet were about 2 fold higher than after the standard SINEMET (Carbidopa-Levodopa) (163 vs 74 ng/mL).

In these studies, using similar total daily doses of levodopa, plasma levodopa concentrations with SINEMET CR fluctuated in a narrower range than with SINEMET (Carbidopa-Levodopa). Because the bioavailability of levodopa from SINEMET CR relative to SINEMET (Carbidopa-Levodopa) is approximately 70-75% the daily dosage of levodopa necessary to produce a given clinical response with the sustained-release formulation will usually be higher.

The extent of availability and peak concentrations of levodopa after a single dose of SINEMET CR 50-200, increased by about 50% and 25%, respectively, when administered with food.

INDICATIONS AND USAGE

SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), postencephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

CONTRAINDICATIONS

Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in patients with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.

WARNINGS

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DOSAGE AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to reach the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskinesias, will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release) than with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are thought to be due to increased brain dopamine following administration of levodopa. All patients should be observed carefully for the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses should be treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodopa).

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bronchial asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS

General As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular, pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS

In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations, while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %	Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %
Dyskinesia	16.5	12.2	Back Pain	1.6	0.6
Nausea	5.5	5.7	Dry Mouth	1.4	1.1
Hallucinations	3.9	3.2	Anorexia	1.2	1.1
Confusion	3.7	2.3	Diarrhea	1.2	0.6
Dizziness	2.9	2.3	Insomnia	1.2	1.0
Depression	2.2	1.3	Orthostatic Hypotension	1.0	1.1
Urinary Tract Infection	2.2	2.3	Shoulder Pain	1.0	0.6
Headache	2.0	1.9	Chest Pain	1.0	0.8
Dream Abnormalities	1.8	0.8	Muscle Cramps	0.8	1.0
Dystonia	1.8	0.8	Paresthesia	0.8	1.1
Vomiting	1.8	1.9	Urinary Frequency	0.8	1.1
Upper Respiratory Infection	1.8	1.0	Dyspepsia	0.6	1.1
Dyspnea	1.6	0.4	Constipation	0.2	1.5
'On-Off' Phenomena	1.6	1.1			

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.
Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.
Digestive: Gastrointestinal pain, dysphagia, heartburn.
Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.
Special Senses: Blurred vision.
Metabolic: Weight loss.
Skin: Rash.
Respiratory: Cough, pharyngeal pain, common cold.
Urogenital: Urinary incontinence.
Musculoskeletal: Leg pain.
Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various cabidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.
Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer.
Cardiovascular: Cardiac irregularities, phlebitis.
Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.
Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protein-bound iodine, Coombs test.

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Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an early sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner's syndrome.
Psychiatric: Delusions, euphoria.
Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.
Metabolic: Weight gain, edema.
Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of hair.
Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.
Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neuroleptic malignant syndrome.

OVERDOSAGE

Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversing the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should be administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted and the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy should be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consideration. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of rats and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant proportion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected to die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases the dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET CR must be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particularly with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. SINEMET CR may be administered as whole or as half-tablets which should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concomitantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patients receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need to be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAGE AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waking day. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*).

A guideline for *initiation* of SINEMET CR is shown in Table II.

TABLE II Guidelines for Initial Conversion from SINEMET (Carbidopa-Levodopa) to SINEMET CR	**SINEMET (Carbidopa-Levodopa)** Total Daily Dose* Levodopa (mg)	**SINEMET CR** Suggested Dosage Regimen
	300-400	1 tab b.i.d.
	500-600	1½ tab b.i.d. or 1 tab t.i.d.
	700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
	900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

*For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations.*

Patients currently treated with levodopa without a decarboxylase inhibitor: Levodopa must be discontinued at least eight hours before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet of SINEMET CR b.i.d.

Patients not receiving levodopa: In patients with mild to moderate disease, the initial recommended dose is 1 tablet of SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon therapeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided doses at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter intervals (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it is recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustment of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can be given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage regimen of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during daytime hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR is required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medication. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to take oral medication.

HOW SUPPLIED

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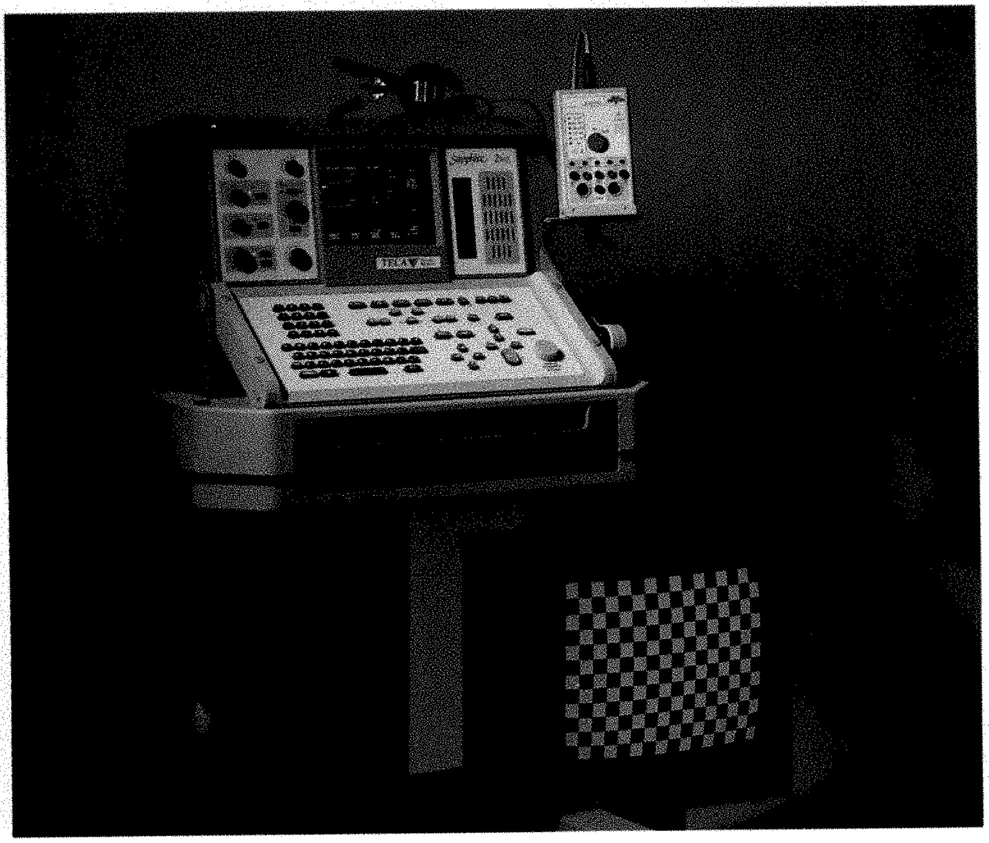

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Vol 48 No. 9 SEPTEMBER 1991

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The Epidemiology of Parkinson's Disease: A Case-Control Study of Young-Onset and Old-Onset Patients 903
Matthew Stern, MD; Eugene Dulaney;
Stephen B. Gruber, PhD, Philadelphia, Pa;
Larry Golbe, MD, Mary Bergen, RN, New Brunswick, NJ;
Howard Hurtig, MD; Steve Gollomp, MD;
Paul Stolley, MD, MPH, Philadelphia, Pa

Clinical and Genetic Analysis of Progressive Dystonia With Diurnal Variation 908
John K. Fink, Ann Arbor, Mich; Paula D. Ravin, Worcester, Mass;
Michelle Filling-Katz; Charles E. Argoff; Mark Hallett, Bethesda, Md

Abnormalities of Cutaneous Blood Flow Regulation in Patients With Reflex Sympathetic Dystrophy as Measured by Laser Doppler Fluxmetry 912
Mark D. Bej, MD, Robert J. Schwartzman, MD, Philadelphia, Pa

Transient Ischemic Attacks With and Without a Relevant Infarct on Computed Tomographic Scans Cannot Be Distinguished Clinically 916
Peter J. Koudstaal, MD, Rotterdam, the Netherlands;
Jan van Gijn, MD, Utrecht, the Netherlands;
Jan Lodder, MD, Maastricht, the Netherlands;
Cor W. G. M. Frenken, MD, Nijmegen, the Netherlands;
Marinus Vermeulen, MD, Rotterdam, the Netherlands;
Cees L. Franke, MD, Heerlen, the Netherlands;
Albert Hijdra, MD, Amsterdam, the Netherlands;
Carel Bulens, MD, for the Dutch Transient Ischemic
Attack Study Group, Rotterdam, the Netherlands

Nuclear Hemodynamic Vertebrobasilar Insufficiency: A New Approach With the Xenon Xe 133 Method 921
Paul Trouillas, MD; Norbert Nighoghossian, MD;
Bernard Philippon, PhD, Lyon, France

Clinical and Morphometric Analysis of the Hypoplastic Corpus Callosum 933
G. Bradley Schaefer, MD, Oklahoma City, Okla;
John B. Bodensteiner, MD, Morgantown, WVa;
James N. Thompson, Jr, PhD, Norman, Okla;
Don A. Wilson, MD, Oklahoma City, Okla

Continued on page 887.

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Alcohol-Induced Brain Changes in Dogs 939
Lawrence A. Hansen, MD, La Jolla, Calif;
Benjamin H. Natelson, MD, Newark, NJ;
Cynthia Lemere, MS, La Jolla, Calif;
Wendell Niemann, DVM, Newark, NJ;
Richard De Teresa, La Jolla, Calif;
Timothy J. Regan, MD, Newark, NJ;
Eliezer Masliah, MD, Robert D. Terry, MD, La Jolla, Calif

Lower Extremity Motor Evoked Potentials in Multiple Sclerosis 944
Seth M. Jones, MD; Leopold J. Streletz, MD; Vicki E. Raab, MD;
Robert L. Knobler, MD, PhD; Fred D. Lublin, MD, Philadelphia, Pa

Frontal Verbal Amnesia: Phonological Amnesia 949
H. Branch Coslett, MD, Philadelphia, Pa; Dawn Bowers, PhD;
Mieke Verfaellie, PhD; Kenneth M. Heilman, MD, Gainesville, Fla

Rapid Recovery From Cortical Visual Impairment Following Correction of Prolonged Shunt Malfunction in Congenital Hydrocephalus 956
Mary B. Connolly, MB, MRCPI, MRCP(UK); James E. Jan, MD, FRCPC;
Douglas D. Cochrane, MD, FRCSC, Vancouver, British Columbia

HISTORY OF NEUROLOGY

A Translation of Otto Binswanger's Article, 'The Delineation of the Generalized Progressive Paralyses' 961
John P. Blass, MD, PhD, White Plains, NY; Siegfried Hoyer, MD,
Roger Nitsch, MD, Heidelberg, Germany

NEUROLOGICAL REVIEW

***N*-Methyl-D Aspartate Antagonists in the Treatment of Parkinson's Disease** 977
J. Timothy Greenamyre, MD, PhD,
Christopher F. O'Brien, MD, Rochester, NY

OBSERVATIONS

Unilateral Oculomotor Palsy and Bilateral Ptosis From Paramedian Midbrain Infarction 983
Grant T. Liu, MD; Enrique J. Carrazana, MD;
Michael E. Charness, MD, Boston, Mass

Marchiafava-Bignami Disease, Syndrome of Interhemispheric Disconnection, and Right-handed Agraphia in a Left-hander 986
A. Rosa, MD; M. Demiati, MD; L. Cartz, MD;
J. P. Mizon, MD, Amiens, France

REGULAR DEPARTMENTS

Instructions for Authors 890

Calendar 894

BOOKS

Advances in Neurology, Parkinson's Disease: Anatomy, Pathology, and Therapy 897
M. B. Streifler; A. D. Korczyn; E. Melamed, M. B. H. Youdin (eds),
Reveiwed by J. Timothy Greenamyre, MD, PhD, Rochester, NY

Neurobehavioral Aspects of Multiple Sclerosis 897
S. M. Rao (ed), Reviewed by George C. Ebers, MD, London, Ontario

Continued on page 888.

ARCHIVES

Avances y Controversias en el Diagnóstico y en el Tratamiento de la Pathologia Vascular Cerebral Isquémica 897
M. Aguilar Barberá; A. Arboix Damunt; L. I. Soler Singlá (eds),
Reviewed by José Biller, MD, Iowa City, Iowa

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Allan E. Rubenstein, Bruce R. Korf (eds),
Reviewed by Gary J. Myers, MD, Rochester, NY

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M. Mumenthaler, H. Schliack (eds),
Reviewed by Peter J. Dyck, MD, Rochester, Minn

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D. G. T. Thomas (ed),
Reviewed by J. Gregory Cairncross, MD, London, Ontario

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Lord Walton (ed),
Reviewed by Alexander G. Reeves, MD, Hanover, NH

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R. C. Griggs, G. Karpati (eds),
Reviewed by Jack E. Riggs, MD, Morgantown, WVa

Post-Polio Syndrome 899
Theodore L. Munsat (ed),
Reviewed by Michael D. Dunn, MD, PhD, Rochester, NY

LETTERS TO THE EDITOR

Delayed Varicella Vasculopathy 900
Grant T. Liu, MD, Boston, Mass
In Reply
A. C. B. Peters, MD, Leiden, the Netherlands

Fetal Homotransplants in the Treatment of Parkinson's Disease 900
Thomas B. Freeman, MD, G. Warren Olanow, MD, Tampa, Fla
In Reply
Ignacio Madrazo, MD, DSc,
Rebecca Franco-Bourland, PhD, Mexico City, Mexico

Psychiatric Effects of Selegiline 902
Sally J. Boyson, MD, Denver, Colo

CORRECTION

Tuberculous Meningitis: Short Course of Chemotherapy 920
Fernando Alarcón, MD; Luis Escalante, MD;
Yanira Pérez, MD; Héctor Banda, MD;
Gonzalo Chácon, MD; Gonzalo Dueñas, MD, Quitor Ecaudor

Index to Advertisers 891

Classified Advertising 989

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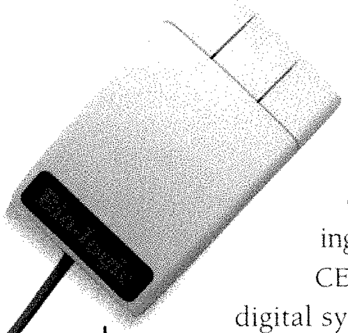

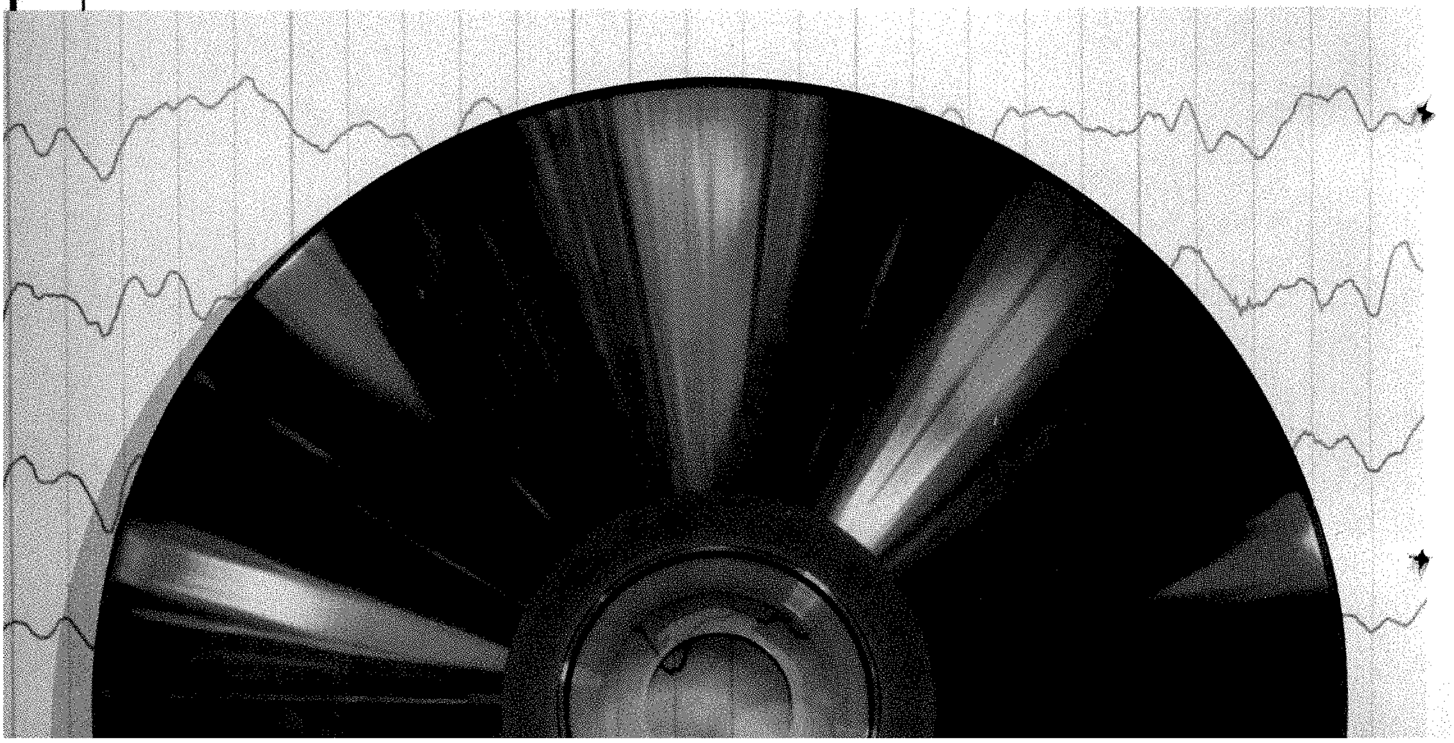

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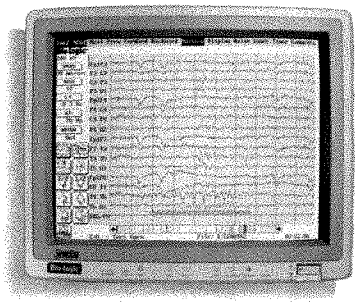

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CALENDAR OF MEETINGS

1991		
Sept	12-15	65th Annual Meeting of the American Thyroid Association, Hyatt Regency Hotel, Boston, Mass. Contact Leonard Wartofsky, MD, Secretary, American Thyroid Association, Endocrine-Metabolic Service, Walter Reed Army Medical Center, Washington, DC 20307-5001; (301) 588-5432.
	29	Eighth Annual Ocular Motor Symposium of the Clinical Eye Movement Society, Seattle, Wash. Contact Stephen E. Thurston, Department of Neurology, Geisinger Clinic, Danville, PA 17821; (717) 271-6278.
Oct	6-12	Eighth Pan-American Congress of Neurology, Montevideo, Uruguay. Contact Carlos Chouza, MD, Congresos SRL, Juncal 1305, Office 1202, 11000 Montevideo, Uruguay.
	8-12	Fifth Annual Meeting of the Pew Neuroscience Program, Ritz Carlton Hotel, Laguna Nigel, Calif. Contact Pew Neuroscience, Meyer 6-109, 600 N Wolfe St, Baltimore, MD 21205; (301) 955-4504.
	13-17	Annual Conference of the International Federation of Multiple Sclerosis Societies, Amsterdam, the Netherlands. Contact C. H. Polman, MD, c/o Free University Hospital, Department of Neurology, PO Box 7057, 1007 MB Amsterdam, the Netherlands.
	14-19	19th International Epilepsy Congress, Rio de Janeiro, Brazil. Contact Congress Secretariat, Rua do Ouvidor 60, Grupo 414, 20040 Rio de Janeiro, Brazil.
	17-20	25th Annual Meeting of the American Medical Electroencephalographic Association, Radisson Plaza Hotel, Minneapolis, Minn. Contact American Medical Electroencephalographic Association, 850 Elm Grove Rd, Elm Grove, WI 53122; (414) 797-7800.
	24-27	Ninth Annual Advanced Neuroradiology Seminar, Hyatt Regency Grand Cypress Resort, Orlando, Fla. Contact Agnes L. Bridges, The Tampa General Hospital, Davis Islands, PO Box 1289, Tampa, FL 33601; (813) 251-7778.
	27-30	10th International Symposium on Parkinson's Disease, Tokyo, Japan. Contact 10th International Symposium on Parkinson's Disease, c/o Japan Convention Services, Nippon Press Center Bldg 4F, 2-2-1 Uchisaiwai-cho, Chiyoda-ku, Tokyo 100, Japan.
	27-Nov 1	Third International Congress of the International Society of Neuroimmunology, Jerusalem, Israel. Contact Secretary, International Society of Neuroimmunology, PO Box 50006, 61500 Tel Aviv, Israel.

POSTHERPETIC NEURALGIA

There Are Many Words To Describe The Pain.

STABBING
PENETRATING
SHARP
JABBING
SHOOTING
UNBEARABLE
PIERCING
GRIPPING
SEARING

And One For Treating It.

Topical
Zostrix®
(Capsaicin 0.025% w/w) Cream

When patients describe the "hurt" of postherpetic neuralgia (PHN), they use a wide range of words to describe a pain that is often intractable and difficult to treat. Zostrix® (Capsaicin 0.025% w/w) Cream provides an effective topical treatment that alleviates intense pain in most PHN patients.

Topical Zostrix Works Where It Hurts

Zostrix®

(Capsaicin 0.025% w/w) Cream

Topical Analgesic

TARGETED ACTION
Acts on sensory nerves at site of application by selectively depleting substance P, a chemomediator of pain impulses along neuropathways.

EFFECTIVE
Alleviates the intense pain associated with postherpetic neuralgia in most patients. May also benefit patients when added to existing systemic drug regimens.

SAFE
No known interactions with systemic medications commonly prescribed for geriatric patients.

Topical Zostrix Works Where It Hurts

DESCRIPTION

Zostrix Cream contains capsaicin, 0.025% w/w, in an emollient base containing benzyl alcohol, cetyl alcohol, glyceryl monostearate, isopropyl myristate, polyoxyethylene stearate blend, purified water, sorbitol solution and white petrolatum. Capsaicin is a naturally occurring substance derived from plants of the Solanaceae family with the chemical name trans-8-methyl-N-vanillyl-6-nonenamide. Capsaicin is a white crystalline powder with a molecular weight of 305.4. It is practically insoluble in water but very soluble in alcohol, ether and chloroform.

ACTION

Although the precise mechanism of action of capsaicin is not fully understood, current evidence suggests that capsaicin renders skin and joints insensitive to pain by depleting and preventing reaccumulation of substance P in peripheral sensory neurons. Substance P is thought to be the principal chemomediator of pain impulses from the periphery to the central nervous system. In addition, substance P has been shown to be released into joint tissues and activate inflammatory mediators involved with the pathogenesis of rheumatoid arthritis.

INDICATION

Zostrix is indicated for the temporary relief of peripheral neuralgias such as the pain following shingles (herpes zoster). Zostrix is also indicated for the temporary relief of the pain associated with rheumatoid arthritis and osteoarthritis.

WARNINGS

FOR EXTERNAL USE ONLY. Avoid contact with eyes and broken or irritated skin. Do not bandage tightly. If condition worsens, or does not improve after 28 days, discontinue use of this product and consult your physician. **Keep this and all drugs out of the reach of children.** In case of accidental ingestion, seek professional assistance or contact a Poison Control Center immediately.

DIRECTIONS

Adults and children 2 years of age and older: Apply Zostrix to affected area 3 to 4 times daily. Transient burning may occur upon application, but usually disappears in 72 hours. Application schedules of less than 3 to 4 times a day may not provide optimum pain relief and the burning sensation may persist. **Wash hands immediately after applying Zostrix.**

HOW SUPPLIED

1.5 oz tube (NDC 52761-552-45)
3.0 oz tube (NDC 52761-552-85)

Store at room temperature.
U.S. Patent Nos. 4486450 and 5536404

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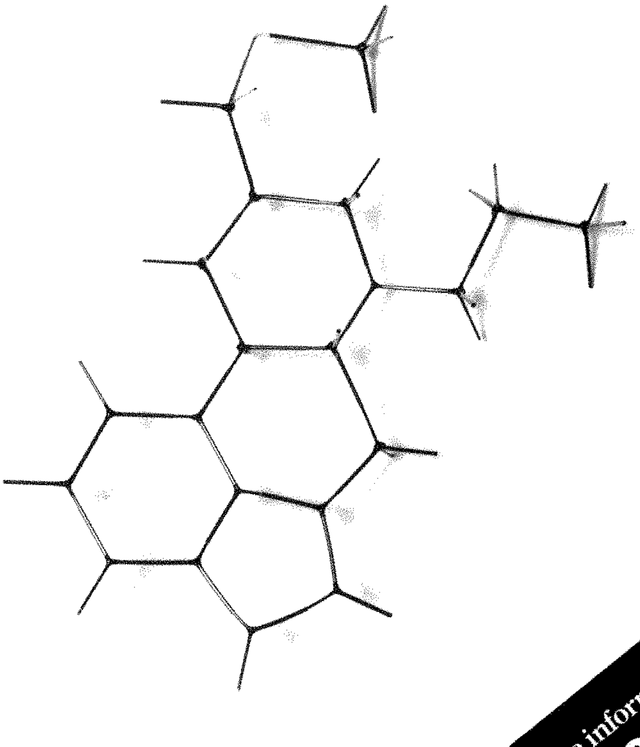
PERMAX®
pergolide mesylate

An adjunct to levodopa/carbidopa treatment in the management of patients with Parkinson's disease



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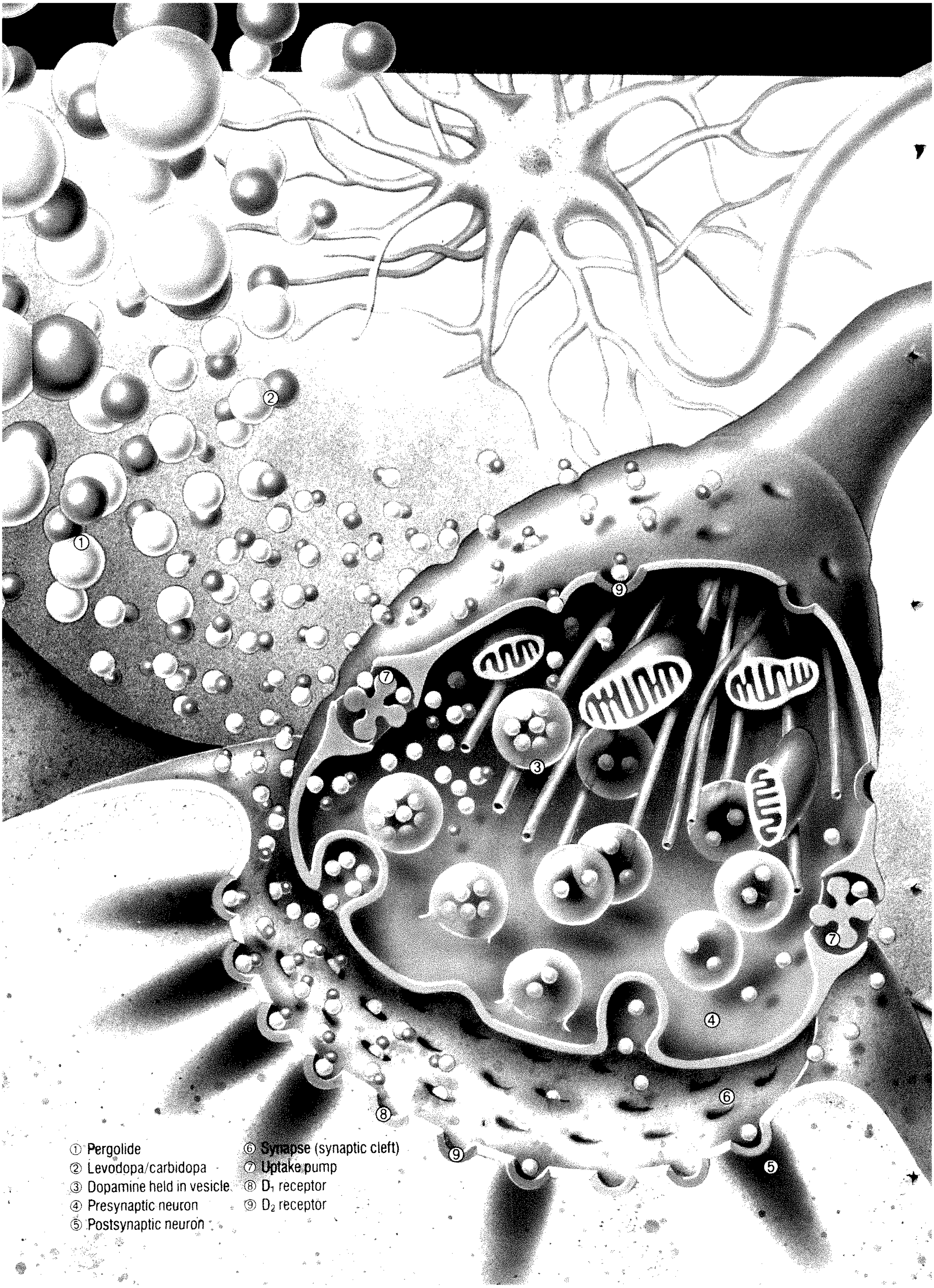
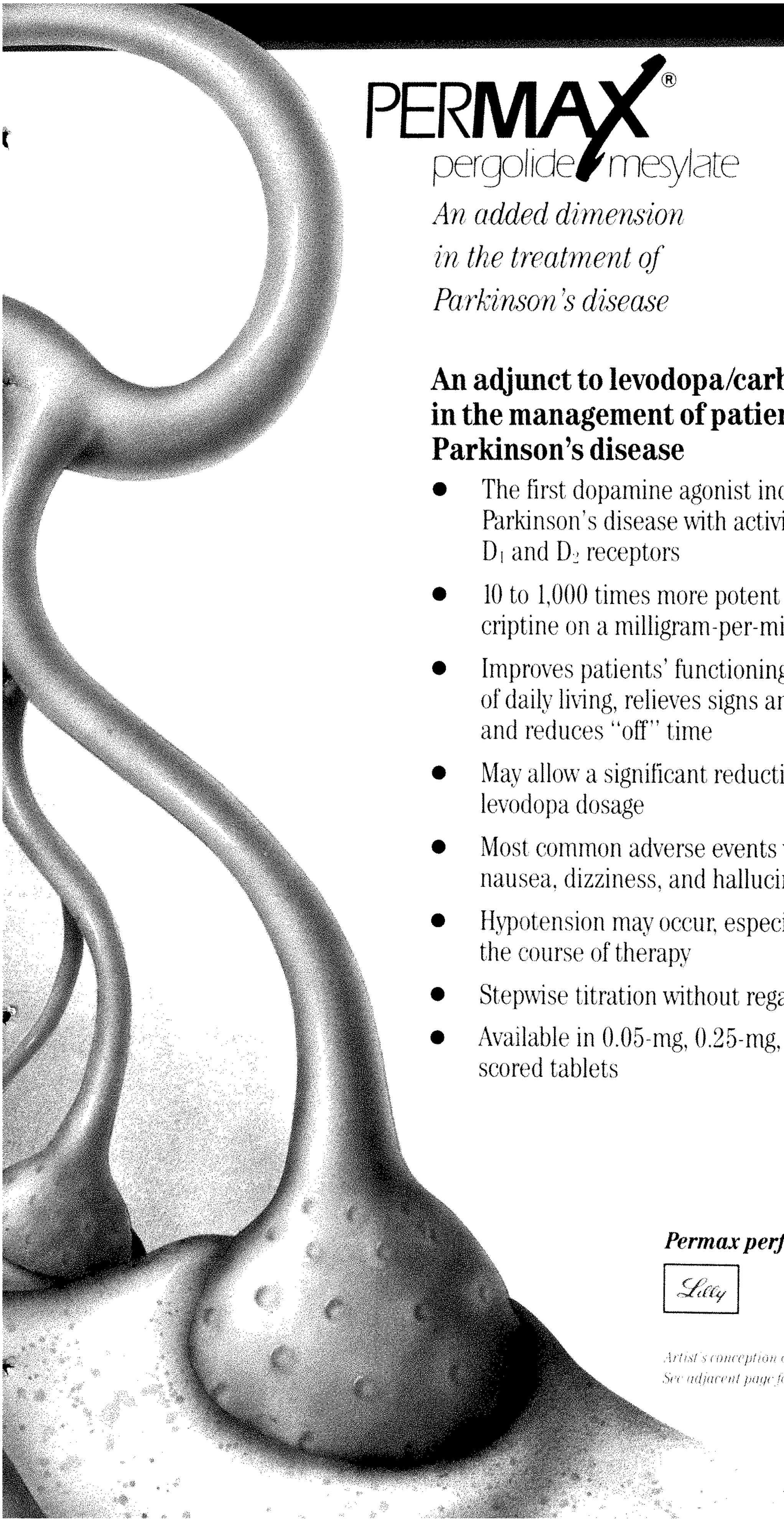
ll free Monday-Friday
AM to 4 PM EST


① Pergolide
② Levodopa/carbidopa
③ Dopamine held in vesicle
④ Presynaptic neuron
⑤ Postsynaptic neuron
⑥ Synapse (synaptic cleft)
⑦ Uptake pump
⑧ D_1 receptor
⑨ D_2 receptor



PERMAX®
pergolide mesylate

An added dimension
in the treatment of
Parkinson's disease

An adjunct to levodopa/carbidopa in the management of patients with Parkinson's disease

- The first dopamine agonist indicated for Parkinson's disease with activity at both D_1 and D_2 receptors
- 10 to 1,000 times more potent than bromocriptine on a milligram-per-milligram basis
- Improves patients' functioning in activities of daily living, relieves signs and symptoms, and reduces "off" time
- May allow a significant reduction in levodopa dosage
- Most common adverse events were dyskinesia, nausea, dizziness, and hallucinations
- Hypotension may occur, especially early in the course of therapy
- Stepwise titration without regard to meals
- Available in 0.05-mg, 0.25-mg, and 1-mg scored tablets

Permax performs

Lilly

Artist's conception of dopamine agonism in the synapse
See adjacent page for prescribing information.

Permax*

pergolide mesylate

Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to levodopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the sample of patients evaluated had been on levodopa/carbidopa for 3.9 years (range, two days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of levodopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy—Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

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There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities —*See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

	Percentage of Patients Reporting Events	
Body System/ Adverse Event*	Pergolide Mesylate N = 189	Placebo N = 187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax —This section reports event frequencies evaluated as of October 1988 for adverse events ocurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System —*Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System —*Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusion, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System —*Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

PA 0913 AMP [102990]

Additional information available to the profession on request.

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Books

Advances in Neurology, vol 53, Parkinson's Disease: Anatomy, Pathology, and Therapy, edited by M. B. Streifler, A. D. Korczyn, E. Melamed, and M. B. H. Youdin, 624 pp, $125, New York, NY, Raven Press, 1990.

Although the title of this book is not inaccurate, it may be somewhat misleading. Rather than being a comprehensive text on Parkinson's disease, it is a collection of almost 90 papers from the Ninth International Symposium on Parkinson's Disease held in Jerusalem, Israel, in June 1988. As such, it probably has little appeal for medical students, nonneurologists, or, possibly, even general neurologists. On the other hand, for those of us with an interest in Parkinson's disease, this book provides a wonderfully diverse smorgasbord of recent clinical and neurobiological research topics related to Parkinson's disease and the basal ganglia.

The papers in this collection are parceled into the following seven sections: "Normal and Pathological Anatomy," "Neurochemistry and Pharmacology," "Neurophysiology," "Toxicology and Environment," "Clinical Aspects," "Current Therapy and Side Effects," and "Therapeutic Research and Developments." The length of the contributions ranges from four to 16 pages and, as might be expected in a collection of this type, they vary in quality. Even though the information in this book is at least 2½ years old at the time of this review, it is surprisingly up to date, especially considering the pace at which research in this field is advancing.

Papers by Graybiel et al and Gibb et al report recent pathologic studies examining the relationship between neuromelanin and selective vulnerability of nigral neurons. The current controversy in this area of investigation is highlighted by the fact that the groups' findings and conclusions are diametrically opposed; the role of melanin remains unclear. The methylphenyltetrahydropyridine (MPTP) model of Parkinson's disease and the mechanism of action of MPTP are the subjects of eight papers. Notably, the International Symposium took place before reports on the defect in complex I of the mitochondrial electron-transport chain had been published, so there is no information on this exciting topic in the book. There are numerous excellent clinical papers dealing with Parkinson's disease and related disorders. A concise and convincing argument for uniform research diagnostic criteria for Parkinson's disease is made by Ward and Gibb. Koller and Findley provide a succinct review of psychogenic tremor, including diagnostic criteria. Several papers discuss the use of deprenyl (Eldepryl) in Parkinson's disease, and Haefely et al discuss the properties of Ro 19-6327, a new, reversible, highly selective monoamine oxidase-B inhibitor that is presently under clinical investigation by the Parkinson Study Group. As might be anticipated, there are four papers on experimental and therapeutic transplantation.

In summary, this volume will be a valuable addition to the libraries of neurologists and neurobiologists interested in recent advances in the pathology, neurochemistry, clinical aspects, and experimental therapeutics of Parkinson's disease and related disorders. It will be less useful for medical students and nonneurologists.

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Neurobehavioral Aspects of Multiple Sclerosis, edited by S. M. Rao, 271 pp, with illus, $39.95, New York, NY, Oxford University Press Inc, 1990.

This small monograph, with contributions by 28 authors, focuses on cognitive and affective alterations in multiple sclerosis (MS). It is divided into four parts: clinicopathological features (84 pages), cognitive dysfunction (91 pages), affective disturbance in MS (35 pages), and management of neurobehavioral dysfunction (52 pages). It is correctly pointed out in the introduction that cognitive dysfunction in MS tends to be overlooked or discounted by physicians. On the other hand, this is often less because of lack of awareness and disinterest and more because of the desire to lighten the already burdensome knowledge of having a disabling neurological disorder. There are situations in which the identification of cognitive impairment in MS is not necessarily to the patient's advantage (eg, custody battles for children). However, the innate variability of human behavior requires a considerable latitude in determining what and how patients should be told about cognitive dysfunction. Furthermore, health professionals need to know the facts in the first place. This book aims at a more complete understanding of behavioral abnormalities in MS and admirably summarizes the rather disparate literature on this topic. The chapters on diagnosis, clinical course, and imaging are certainly not definitive but give readable and concise surveys. The chapter on subcortical dementia appears to perpetuate the long-standing and erroneous assumption that MS does not involve the cerebral cortex. The chapters on memory, cognitive dysfunction, and affected disturbance constitute an excellent synthesis and summary of the present state of knowledge. The long-standing debate on the role of stress in MS is ably reviewed by Warren.

The book is directed toward the multidisciplinary audience, a daunting task in which it succeeds well. It serves to illustrate the necessity for a multidisciplinary approach in the comprehensive management of a patient with MS. It should make worthwhile reading for neurologists, psychiatrists, neuropsychologists, and other health care professionals who see substantial numbers of patients with MS.

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Avances y Controversias en el Diagnóstico y en el Tratamiento de la Pathologia Vascular Cerebral Isquémica, edited by M. Aguilar Barberá, A. Arboix Damunt, L. I. Soler Singlá, Barcelona, Spain, Edika Medica SA, 1989.

This volume represents a compilation of papers presented at the International Symposium on Ischemic Cerebrovascular Pathology held by the Societat Catalana de Neurologia in Tarragona, Spain, in 1989.

The volume opens, with the only chapter written in English, on selected aspects of human and experimental stroke. Subsequent chapters contain a number of relevant topics related to diagnostic, pathologic, and therapeutic aspects of ischemic cerebrovascular disease. There are interesting contributions on the local and regional strategies regarding care services for patients with acute stroke. Another chapter summarizes a discussion on vascular dementias and brain-heart interactions.

The book is well written, easy to read, and most sections are clearly organized and referenced. Although much of the information presented is well known, the chapters serve as useful review. Overall, controversial points are presented in a well-balanced manner. Like many published reports of conference proceedings, this volume suffers from an uneven quality of the contributions.

All in all, any clinician who regularly takes care of patients with stroke will find this volume helpful and informative.

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Neurofibromatosis: A Handbook for Patients, Families, and Health Care Professionals, edited by Allan E. Rubenstein and Bruce R. Korf, 256 pp, with illus, $63, New York, NY: Thieme Medical Publishers Inc, 1990.

In recent years, our knowledge of neurofibromatosis (NF) has expanded significantly. The location of the NF gene on chromosome 17, for NF 1, and chromosome 22, for NF 2, has been identified, and the clinical variations of the disorder have been more fully delineated. The book was sponsored by the National Neurofibromatosis Foundation, New York, NY, and the approach is varied, with some information written for the layperson and other topics more detailed and professionally oriented. The book is multiauthored and brings together the existing information about NF as of early 1990. It is divided into four sections: "Medical," "Genetic," and "Psychosocial Aspects," and "Appendices." There are 20 chapters covering most of the major areas of concern. Following the introduction and history, there are chapters on diagnosis, neurological aspects, ocular features, NF and cancer, molecular genetics, psychosocial aspects, and many other areas. The chapter organization makes it easy to find information on any subject of interest. The book is filled with useful information, and each chapter is well referenced. The appendix contains information on the National Neurofibromatosis Foundation and a listing of their chapters, along with NF clinics and centers in the United States and Canada.

An effort is made to make material understandable to the layperson, but there is also an effort to be comprehensive and accurate. The authors avoid any dogmatic approach to therapy or standardized follow-up and repeatedly emphasize the importance of evaluating each person individually and using clinical judgment.

The book is well illustrated, attractive, and easy to read. There are numerous tables that outline diagnostic criteria and complications. The myriad of these complications that can or might occur with NF are carefully detailed by multiple authors. Repeatedly, these authors comment that the percentage of patients who have these complications is small, but it is page 176 before Dr Carey states that "more than half of all people with NF will only have café au lait spots and cutaneous neurofibromas. The remaining 30% to 40% of individuals will have one or more of the more medically serious complications. . . . " In a book for patients and families, some might be very anxious by the time they reach this reassuring information.

I found it an excellent overview of NF for health care professionals and can recommend it to them. It will also be helpful to families and patients if it is combined with counseling from knowledgeable professionals or the national organization. It provides a handy source of information for anyone working with individuals who have this complex disorder.

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Peripheral Nerve Lesions, edited by M. Mumenthaler and H. Schliack, 416 pp, with illus, $95, New York, NY, Thieme Medical Publishers Inc, 1991.

This 400-page book, mostly on focal peripheral nerve lesions and their treatment, is the "revised translation (Sibylle A. Wallace, pediatric neurologist, Mount Sinai School of Medicine [New York, NY]) from the [fifth] German edition, published and copyrighted in 1987."

The book is logically organized with sequential sections on nerve embryology, anatomy, histopathology, classification of traumatic lesions, biomechanics, physiology, clinical examination, electrophysiologic examination, and operative treatment, and followed by specific sections on roots, plexus, and peripheral nerves. At least four major books on this subject are now in print, several written by orthopedists. In comparison with these other books, this one has approximately the same number of pages but contains more information. It is a scholarly work with extensive references. It has many line drawings, generally of reasonable quality. Because it is comprehensive, compact, well-referenced, and authoritative, it can be recommended with considerable enthusiasm.

The book has weaknesses too. Too frequently, pseudoscientific expressions are used instead of simple descriptions. Patients do not "complain of brachialgia paresthetic nocturna." Presumably, the translator was trying to convey the author's precise meaning, but too often the sentences are long, heavy, and not illuminating. The illustrations also are not always the best. Some of the old illustrations should have been replaced by new and better ones. Why, for example, are we not shown a magnetic resonance scan of a synovial cyst compressing the peroneal nerve? Perhaps the greatest weakness of the book is that it insufficiently focuses on unsolved problems. Our ignorance of underlying pathophysiologic mechanisms is not emphasized. Although this book has sections on neurobiology and neuropathology, it is unclear how they might help resolve some of the clinical problems. Important new insights have been gained in how nerves react to compression and of how fibers regenerate, or do not, depending on species, site, nature of lesion, and a variety of other risk factors.

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Neuro-Oncology: Primary Malignant Brain Tumors, edited by D. G. T. Thomas, 303 pp, $62.50, Baltimore, Md, The Johns Hopkins University Press, 1990.

Thomas and 24 contributors set out to write a thorough, authoritative, contemporary text on primary malignant brain tumors for postgraduate clinicians and basic scientists interested in neuro-oncology. By and large, they have succeeded. The book is certainly thorough, containing chapters on clinical manifestations, epidemiology, imaging, pathology, treatment, relevant basic sciences, and terminal care of patients with brain tumor. The chapter by Thomas and McKeran, "Clinical Manifestations of Brain Tumors," is appropriate for students but seems out of place in a book intended for a neurologically sophisticated audience. The chapter on biological response modifiers is too long and needs a discussion of adrenocorticosteroid therapy for patients with brain tumor. The book is authoritative with contributions by many leading investigators, including an outstanding chapter on "Radiotherapy in the Treatment of Cerebral Astrocytomas" by Leibel and Sheline. The book is not entirely up-to-date, but this, of course, is the Achilles' heel of any text. For example, the discussion of tumor-suppressor genes (ie, antioncogenes) as they pertain to the genesis and progression of glioma is deficient by 1991 standards, unfortunate because the chapter on molecular genetics by Westermark et al is splendid otherwise. Similarily, the concise, thoughtful contribution by Dropcho and Mahaley on

"Chemotherapy for Malignant Glioma in Adults" is not current, missing several recent references to successful chemotherapy for specific malignant glioma subtypes. If the chapter on clinical manifestations of brain tumor is included in future editions, the tables should be updated. They are taken from an article published before the modern computed tomographic and magnetic resonance era (eg, a diagnosis of papilledema diagnosis in 52% of cases). Like most multiauthored books, duplications and omissions are present, but, to his credit, Thomas, by careful editing, has managed to keep both to a minimum. May I suggest the next edition of this text be renamed "Neuro-Oncology: Glioma" and the content focused accordingly? Alternatively, the title may be maintained and the content expanded to include certain malignant brain tumors omitted from this edition (eg, primary cerebral lymphoma and malignant meningioma).

The strengths of this text far outweigh its weaknesses. It is a valuable reference text in its current form, and I look forward to future editions.

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Essentials of Neurology, ed 6, edited by Lord Walton, 339 pp, $33, New York, NY, Churchill-Livingstone Inc, 1989.

That a book can go through six editions speaks to some degree for its quality.

Essentials of Neurology continues to be a good book. It is not extensive enough to be a reference and not oriented toward pathophysiology, so it cannot be considered a basic text for students. It is predominantly a primer of the phenomenology of clinical neurology; an elaboration of basic principles of evaluation of the nervous system with an overview of the major entities (systems, signs, and broad disease categories).

The audience should be the resident in internal medicine, the primary physician, and, possibly, also the beginning neurology resident. The text is more extensive than past editions but appears not much larger, probably because of the reduction in the size of the print; it is fortunate that youngsters with good eyes will be the main audience.

The motivated trainee will find this book a good starter and, it is hoped, will be stimulated to delve deeper into more extensive sources for the specifics.

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Myoblast Transfer Therapy, vol 280, **Advances in Experimental Medicine and Biology,** edited by R.C. Griggs and G. Karpati, 316 pp, with illus, $79.50, New York, NY, Plenum Press, 1990.

Myoblast transfer represents an early exploitation in a therapeutic venture based on the tremendous advances made by molecular genetics. The possibility and promise of myoblast transfer therapy in the treatment of Duchenne muscular dystrophy and other inherited forms of muscle disease has raised the hopes and expectations of the public and, especially, affected individuals and their families.

This volume, a compilation of 35 presentations made at the International Conference on Myoblast Transfer Therapy in June 1989, is conveniently organized into seven general-topic sections relevant to myoblast therapy. The individual articles, which are well-written, short, and focused, present a realistic assessment of the challenges that will need to be addressed and mastered before myoblast transfer therapy can ever become "standard therapy." The discussions that follow individual articles and each general-topic section are very enlightening as they highlight many of the practical concerns and unresolved questions regarding myoblast transfer therapy.

The reader will find that this book successfully separates the science fiction from the fact associated with myoblast transfer. Therefore, clinicians who regularly care for and thus serve as medical interpreters for patients with muscle disease and their families would find this volume extremely useful. Historically, this volume provides a succinct but comprehensive snapshot of current scientific understanding in an exciting area of medicine, at a juncture when advances in molecular genetics are being initially applied to novel therapeutic techniques.

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Post-Polio Syndrome, edited by Theodore L. Munsat, 121 pp, with illus, $44.95, Boston, Mass, Butterworth-Heinemann, 1991.

This volume represents a concise collection of useful information on the so-called post-polio syndrome, a somewhat poorly understood disorder leading to disability many years after acute poliomyelitis. The emphasis of each chapter varies, and it will be helpful to physiatrists, neurologists, orthopedists, physical therapists, and sufferers themselves.

This book has 10 chapters. The first represents a general introduction with some historical notes. The second chapter discusses basic molecular biology and virology. The fourth chapter is also primarily basic science, dealing with the pathology of muscle and spinal cord in both acute poliomyelitis and the post-polio syndrome. The third chapter is more clinically oriented, giving a general definition of the post-polio syndrome and describing clinical features. Chapters 5 and 6 deal primarily with the electrophysiology of the syndrome, including electromyography, single-fiber electromyography, and macroelectromyography. Some discussion of muscle biopsy is also included. Chapter 7 is once again more clinically oriented with the discussion of strength measurement. The eighth chapter, by a physical therapist, deals with rehabilitation. This is quite good but, unfortunately, somewhat too short. Chapters 9 and 10 are written by survivors of poliomyelitis who have been active in the effort to educate not only other survivors of the disease but also the medical community.

The strengths of the book depend on the interest of the reader. For basic scientists or researchers, chapters 4 through 6 on pathology and electrophysiology are quite good and review all significant investigations to date. For the clinically minded, chapters 3 and 7 are excellent. For the poliomyelitis survivor, the chapters on history and rehabilitation are of interest. Also, the last two chapters on support groups and community resources could be quite helpful. The illustrations and tables are generally concise and organized. References are extensive.

This book is somewhat lacking in several areas. No adequate discussion is presented of the long-term orthopedic complications of poliomyelitis, which certainly can be regarded as a manifestation of the post-polio syndrome. The excellent chapter on rehabilitation is too short and not detailed enough. No emphasis is placed on issues of differential diagnosis, as many of the symptoms of post-polio syndrome are vague and can mimic those of a variety of other medical illnesses. This is quite important in that treatable illness should not be overlooked and ascribed to old poliomyelitis. Finally, by virtue of having multiple authors, material is unduly repeated.

In summary, this volume represents a valuable, concise resource for medical practitioners in a variety of disciplines who are exposed to patients with the late effects of poliomyelitis. It also should be a valuable reference for patients themselves.

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Letters to the Editor

Letters to the editor should be submitted as an original and two duplicates. They should be typewritten double-spaced on plain bond paper; they will be subject to editing. If they are prepared on a word processor, do not justify the right margin. A copyright transmittal letter signed by all authors must accompany this (see "Instructions for Authors").

Delayed Varicella Vasculopathy

To the Editor.—I read with great interest the article by Caekebeke et al.[1] They carefully document a case of a 5-year-old boy who suffered from an acute hemiparesis 3 and 9 months after a chickenpox infection.

However, I disagree with their contention that this association had not been previously reported. Earlier, Holmes and I[2] described a 3½-year-old boy who developed a hemiparesis 1 month after a varicella infection. Eda et al[3] in 1983 had already reported four similar cases, and then Kamholz and Tremblay[4] documented another. The ages of the six patients[2-4] ranged from 1 to 6 years of age, and the time between onset of varicella and onset of hemiparesis varied from 1 to 3 months. Cranial imaging studies revealed infarcts involving the basal ganglia and internal capsule in all six cases. Caekebeke and coworkers' patient[1] differs slightly because he had two events at 3 and 9 months after varicella infection, and his infarct involved the left putamen as well as the left temporal lobe.

Their statement that acute childhood hemiplegia was not a known complication of zoster infection is also incorrect. Walker et al[5] described a 7-year-old boy with herpes zoster ophthalmicus and contralateral hemiplegia; his angiogram showed multiple areas of narrowing in the proximal anterior and middle cerebral arteries.

By documenting intrathecal synthesis of varicella zoster virus IgG and IgA in addition to abnormalities in the magnetic resonance image and cerebral angiogram, Caekebeke et al[1] have described their patient in more detail than any of the previously reported cases. Theirs is, therefore, the most convincing. However, they are not the first authors to describe this association between varicella and a delayed hemiparesis.

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1. Caekebeke JFV, Boudewyn Peters AC, Vandvik B, Brouwer OF, de Bakker HM. Cerebral vasculopathy associated with primary varicella infection. *Arch Neurol.* 1990;47:1033-1035.
2. Liu GT, Holmes GL. Varicella with delayed contralateral hemiparesis detected by MRI. *Pediatr Neurol.* 1990;6:131-134.
3. Eda I, Takashima S, Takeshita K. Acute hemiplegia with lacunar infarct after varicella infection in childhood. *Brain Dev.* 1983;5:494-499.
4. Kamholz J, Tremblay G. Chickenpox with delayed contralateral hemiparesis caused by cerebral angiitis. *Ann Neurol.* 1985;18:358-360.
5. Walker RJ, Gammal TE, Allen MB. Cranial arteritis associated with herpes zoster: case report with angiographic findings. *Radiology.* 1973;107:109-110.

In Reply.—Dr Liu is correct: we missed earlier reports on the association between chickenpox and acute hemiparesis in childhood. Recently, another case was described by Shuper et al.[1] This 7.5-year-old boy developed a right hemiplegia and aphasia 10 weeks after contracting chickenpox. He presented again 7 months later with an acute exacerbation of seizures. Cerebral angiography showed evidence of focal vasculitis.

The presumed association of primary varicella zoster virus infection and vasculitis rests on the temporal occurrence and on the demonstration of an intrathecal varicella zoster virus-specific IgG response. However, oligoclonal bands can still be demonstrated several months after an uncomplicated varicella zoster virus meningitis and do not provide definite evidence for active infection.[2] Definite proof of the linkage between primary varicella zoster virus infection and vasculitis can only be obtained by cerebral biopsy, which is not indicated in these patients, or by an autopsy.

In clinical practice, physicians facing a child with an acute hemiparesis should carefully ask about a history of antecedent chickenpox. The management in these varicella zoster virus-associated cases is still open: steroids, acyclovir, or no medication at all?

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1. Shuper A, Vining EPG, Freeman JM. Central nervous system vasculitis after chickenpox: cause or coincidence? *Arch Dis Child.* 1990;65:1245-1248.
2. Kostulas VK, Link H, Lefvert AK. Oligoclonal bands in cerebrospinal fluid. *Arch Neurol.* 1987;44:1041-1044.

Fetal Homotransplants in the Treatment of Parkinson's Disease

To the Editor.—The article by Madrazo et al[1] represents an analysis of seven patients who underwent embryonic nigral and adrenal transplants for the treatment of Parkinson's disease. We note that donor neuronal tissue used for this study was derived from spontaneous abortions. There are several problems associated with the use of tissue obtained from spontaneous as opposed to elective abortion for use in neural grafting. These include the following:

1. Chromosomal abnormalities are present in 20% to 50% of cases of spontaneous abortion.[2]
2. Infectious agents that are associated with spontaneous abortions may increase the risk of a transplant-related infection.[3]
3. There is an increased likelihood of bacterial contamination in donor material obtained at the time of spontaneous abortion due to the direct passage of the fetus through the vaginal canal. In elective abortions there is a high likelihood that tissue can be procured steriley.[4,5] In this regard, one wonders if the brain abscess and bone flap infections in patient number three were not transplant derived rather than a consequence of immunosuppression as the authors suggest. Information regarding the type of organism and the exact location of the brain abscess might help in clarifying this issue.
4. The majority of spontaneous abortions are preceded by fetal death in utero, which substantially reduces the likelihood of obtaining a viable graft.[6,7]

5. Spontaneous abortions are frequently associated with fetuses that are abnormally small, making staging difficult.[8]
6. Central nervous system defects are frequently associated with spontaneous abortions.[8]
7. Spontaneous abortions occur unpredictably making the timing of the surgical procedure and serological testing for human immunodeficiency virus, hepatitis, cytomegalovirus, and herpes in both the mother and fetus logistically difficult.
8. The authors employed ventral mesencephalon from only one fetus per patient. Pharmacologic analyses of the human striatum suggest that multiple donors (three to four) are necessary in order to provide sufficient concentrations of dopaminergic neurons to obtain the desired clinical effect.[4] Elective abortions provide a better opportunity to procure tissue from multiple donors.

The age of the donor also appears to be critically related to the likelihood of graft survival.[9] The optimal period for transplantation is thought to occur during the period of dopaminergic neuronal development and migration, but before the period of axonal extension.[9] This period of development occurs in the human embryo between postconception weeks 6.5 and 8.0.[10-12] Both solid and suspension grafts are most likely to be viable when tissue is derived from this period.[11,13] Madrazo used solid transplants derived from donors age postconception week 11 to 12. There is no laboratory data to the best of our knowledge that indicates that there is significant survival of dopamine neurons in human grafts of the age used in this study. Further, it is not clear how the embryonic age was determined. It should be noted that if dating is based on maternal record of last menstrual period, it is frequently inaccurate.[14]

There are several additional points that cause us to question whether the benefits reported from this procedure are due to some other mechanism such as the release of trophic factors.[15] The initial clinical improvement occurred between 4 and 8 weeks after transplantation. This is more rapid than would be expected if improvement were due to neuronal outgrowth of dopaminergic neurons.[13] Both dopaminergic- and nondopaminergic-mediated symptoms are reported to have improved. The graft was placed into the caudate nucleus, which is thought to have less influence than the putamen on dopaminergically mediated motor abnormalities of Parkinson's disease.[16] The time course of improvement parallels that observed in patients following autologous adrenal transplants where graft survival has been notably poor.[17,18] Finally, the best results were obtained in patients who received grafts derived from the oldest donors, which are the grafts least likely to survive.

On the other hand, if the benefits observed are the result of the elaboration of dopamine and neuronal connections from grafted cells, then based on such scientific evidence as currently exists, it is reasonable to suspect that transplantation of a larger number of younger fetuses obtained from women undergoing voluntary abortions may provide further clinical improvement.

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1. Madrazo I, Franco-Bourland R, Ostrosky-Solis F, et al. Fetal homotransplants (ventral mesencephalon and adrenal tissue) to the striatum of parkinsonian subjects. *Arch Neurol.* 1990;47:1281-1285.

2. Warburton D, Stein Z, Kline J, Susser M. Chromosome abnormalities in spontaneous abortion. In: Porter IH, Hook B, eds. *Human Embryonic and Fetal Death.* Orlando, Fla: Academic Press Inc; 1980:261-287.

3. Sever JL. Infectious cause of human reproductive loss. In: Porter IH, Hook B, eds. *Human Embryonic and Fetal Death.* Orlando, Fla: Academic Press Inc; 1980:169-175.

4. Lindvall O, Rehncrona S, Brudin P, et al. Human fetal dopamine neurons grafted into the striatum in two patients with severe Parkinson's disease. *Arch Neurol.* 1989;46:615-631.

5. Dumez Y, Oury JF. Method for first trimester selective abortion in multiple pregnancy. *Contr Gynecol Obstet.* 1986;15:50-53.

6. Huisjes, HJ. Spontaneous Abortion. In: Lind T, ed. *Current Reviews in Obstetrics and Gynecology.* New York, NY: Churchill-Livingstone, Inc; 1984:34.

7. Strobino B, Pantel-Silverman J. First trimester vaginal bleeding and the loss of chromosomally normal and abnormal conceptions. *Am J Obstet Gynecol.* 1987;157:1150-1154.

8. Nishimura H, Tarano K, Tanimura T, Yasuda M. Normal and abnormal development of human embryos: first report of the analysis of 1213 intact embryos. *Teratology.* 1968;1:281-290.

9. Bjorklund A, Stenevi U, Schmidt RH, Dunnett SB, Gage FH. Intracerebral grafting of neuronal cell suspension, I. introduction and general methods of preparation. *Acta Physiol Scand.* 1983(suppl 522):1-7.

10. Freeman T, Spence MS, Miao R. Development of tyrosine hydroxylase positive neurons in the human fetal substantia nigra. Third International Symposium on Neural Transplantation. *Restor Neurol Neurosci.* 1989;1:155-156.

11. Freeman TB, Kordower J. Human cadaver embryonic substantia nigra grafts: effects of ontogeny, preoperative graft preparation and tissue storage. In: *Intracerebral Transplantation in Movement Disorders: Experimental Basis and Clinical Experience.* Amsterdam, the Netherlands: Elsevier Science Publishers. In press.

12. Freeman TB, Spence MS, Boss BD, et al. Development of dopaminergic neurons in the human substantia nigra. *Exp Neurol.* In press.

13. Brudin P, Nilsson OG, Strecker RE, Lindvall O, Astedt B, Bjorklund A. Behavioral effects of human fetal dopamine neurons grafted in a rat model of Parkinson's disease. *Exp Brain Res.* 1986;65:235-240.

14. Drumm JE, O'Rahilly R. The assessment of prenatal age from the crown-rump length determined ultrasonically. *Am J Anat.* 1977;148:555-560.

15. Bohn MC, Cupit L, Marciano F, Gash DM. Adrenal medulla grafts enhance recovery of striatal dopaminergic fibers. *Science.* 1987;237:913-916.

16. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. *Annu Rev Neurosci.* 1986;9:357-381.

17. Goetz CG, Olanow CW, Koller WC, et al. Multicenter study of autologous adrenal medullary transplantation to the corpus striatum in patients with advanced Parkinson's disease. *N Engl J Med.* 1989;320:337-341.

18. Jankovic J, Grossman R, Goodman C, et al. Clinical biochemical and neuropathologic findings following transplantation of adrenal medulla to the caudate nucleus for treatment of Parkinson's disease. *Neurology.* 1989;39:1227-1234.

In Reply.—We appreciate Freeman and Olanow's comments to our recent article on fetal brain homotransplantation for the treatment of Parkinson's disease (PD).[1] In relation to their concern for our use of fetal tissue obtained from spontaneous abortions for neural grafting, as opposed to elective abortions, we are in complete agreement with their arguments favoring elective abortions as a source of fetal tissue. In Mexico, however, we are limited to the use of fetuses only from spontaneous abortions, because elective abortions are illegal. We realize the complexity and multiple drawbacks involved, but have found this to be our only alternative for obtaining human fetal tissue in order to start the development of human fetal-human brain transplantations. We encourage those neural transplantation groups in countries where elective abortions are legal, to take advantage of their social circumstance, and thereby avoid the biological shortcomings that Freeman and Olanow enlisted in their letter.

Regarding the use of tissue from only one fetus, we[1] and others[2-6] have found this amount of unmanipulated tissue to give clinical benefit to the patients. Also, the immunologic challenge to the host is obviously less than would be expected from the use of tissue from more donors. The infection in patient number three is unlikely to be derived from the transplant, because it clearly started on the bone flap.

The viability and age of the fetuses were determined by in utero ultrasonography performed at the time abortion was diagnosed as imminent by the gynecologist who was unrelated to our transplantation group. Regarding the survival of dopamine neurons in fetal human grafts of 13 to 14 weeks' gestational age, there is neuropathologic evidence of their survival after human brain transplantation.[6]

The clinical response to fetal brain transplantation is good evidence of the probable relevance and interrelationship of all known mechanisms of action (local release of neurotransmitters, trophism, conectivity, etc.) of brain grafting procedures in the effectiveness of neural grafting. The possible therapeutic value of the different grafts is apparent from the evident differential clinical responses seen in our different groups of autotransplanted and homotransplanted parkinsonian subjects.[7]

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1. Madrazo I, Franco-Bourland R, Ostrosky-Solis F, et al. Fetal homotransplants (ventral mesencephalon and adrenal tissue) to the striatum of parkinsonian subjects. *Arch Neurol.* 1990;47:1281-1285.
2. Freed CR, Breeze RE, Rosenberg NL, et al. Transplantation of human fetal dopamine cells for Parkinson's disease: results at 1 year. *Arch Neurol.* 1990;47:505-512.
3. Molina H and the Neurotransplantation Group. Clinical results: the Cuban experience. Neurotransplantation in Parkinson's disease. Presented at the Eric K. Fernstrom Symposium. Intracerebral transplantation in movement disorders: experimental basis and clinical experiences. Lund, Sweden, June 20-22, 1990.
4. Lopez-Lozano JJ, Bravo G, Uria J, et al. CPH Neural Transplantation Group: Spanish experience in implants of fetal ventral mesencephalon into Parkinson's patients. Presented at the Eric K. Fernstrom Symposium. Intracerebral transplantation in movement disorders: experimental basis and clinical experiences. Lund, Sweden, June 20-22, 1990.
5. Hitchcock E, Clough C, Hughes R, Kenny B, Henderson B, Detta A. Clinical results: the British experience. Presented at the Erick K. Fernstrom Symposium. Intracerebral transplantation in movement disorders: experimental basis and clinical experiences. Lund, Sweden, June 20-22, 1990.
6. Dymecki J, Zabek M, Mazurowski W, Kuran W, Kulczycki G. Treatment of Parkinson's disease. Presented at the Erick K. Fernstrom Symposium. Intracerebral transplantation in movement disorders: experimental basis and clinical experiences. Lund Sweden, June 20-22, 1990.
7. Madrazo I, Franco-Bourland R, Ostrosky-Solis F, et al. Neural transplantation (auto-adrenal, fetal nigral, and fetal adrenal) in Parkinson's disease: the Mexican experience. *Progr Brain Res.* 1990;82:593-602.

Psychiatric Effects of Selegiline

To the Editor.—The exciting news that selegiline (deprenyl, Eldepryl) may retard the progression of early Parkinson's disease,[1,2] accompanied by the observation that few significant adverse effects were observed in these studies, has led physicians to treat many of their Parkinson's disease patients with this drug. This report concerns adverse psychiatric effects seen in my referral population of patients with Parkinson's disease. Over the last year, we have started selegiline therapy in approximately 60 patients, almost all of whom were both on multiple other antiparkinsonian medications and known to me for some time prior to this treatment. I have not included adverse effects that could be ameliorated by reduction of the dose of carbidopa/levodopa.

Apparent adverse effects in the younger population were most common in physically small patients, especially women. Five otherwise healthy women in their 40s and 50s developed adverse effects, although only two of these had a prior psychiatric history. All were taking carbidopa/levodopa. Three women (ages 41, 46, and 46 years, respectively) became hypomanic, with racing thoughts, mild paranoia, and markedly reduced sleep. Two women almost lost their jobs because of these changes. One woman who became promiscuous as well had a prior history compatible with cyclothymia, but had never been treated for this. In these three patients, the symptoms abated with lowering the dosage to 2.5 to 5 mg/d.

Two women became psychotic. A 48-year-old woman was taking multiple other antiparkinsonian medications and had a prior history of psychiatric hospitalization. She became floridly psychotic with organized and tenacious delusions and paranoia 3 months after selegiline was added, in the absence of other drug changes; the patient remained psychotic for 1 year. The last woman, aged 53 years, was seen by us after becoming floridly manic and psychotic soon after beginning selegiline therapy for very mild parkinsonism and was still hospitalized and psychotic 6 months after discontinuation of selegiline. She also had a history compatible with, but not diagnosed as, cyclothymia.

In the elderly, adverse psychiatric effects were most commonly seen in patients with some evidence of dementia. Several men who had behavioral problems with inappropriate and aggressive verbal remarks became more verbally abusive to their caretakers. Reversal of sleep-wake cycles was also exacerbated, with an increase in nocturnal activities. One 78-year-old man who had had a stable relationship with one woman for several years suddenly began to make sexual advances to other women.

While the increased aggressiveness in demented patients could have been predicted from responses in this population to other dopaminergic agents, the dose-related hypomania in otherwise healthy young women was unexpected. The hypomania may well be due to the L-amphetamine and L-methamphetamine metabolites of selegiline. Although the L-isomers are far less potent than the D-isomers, it is possible that these women had greater synthesis or decreased clearance of these metabolites so that effective blood levels were reached on a standard dose of 10 mg/d of selegiline.

We have revised our prescribing practice to employ gradual upward titration of the dose, from 2.5 mg/d to 10 mg/d over 10 to 15 days, in all patients. If patients experience significant potentiation of dopaminergic effects or signs of hypomania at a dose lower than 10 mg/d, the dose is not increased further. We no longer prescribe selegiline for significantly demented patients, and prescribe this with caution in patients with a history of cyclothymia.

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1. The Parkinson Study Group. Effects of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1989;321:1364-1371.
2. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science.* 1989;245:519-545.

Original Contributions

The Epidemiology of Parkinson's Disease

A Case-Control Study of Young-Onset and Old-Onset Patients

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• While the cause of Parkinson's disease (PD) remains unknown, recent evidence suggests that certain external factors, ie, environmental agents, may act as neurotoxins, initiating the chain of oxidative reactions that ultimately destroy neurons in the substantia nigra. Young-onset PD might result from greater exposure to a putative neurotoxin. This hypothesis has rekindled interest in the epidemiology of PD. We therefore conducted a detailed analysis of various environmental exposures and early life experiences in 80 patients with old-onset PD (at an age older than 60 years), 69 young-onset patients (younger than 40 years), and 149 age- and sex-matched control subjects. Contrary to previous reports, we were unable to implicate well water or exposure to herbicides, pesticides, or industrial toxins as significant PD risk factors. A residential history of rural living was reported by more patient cases than control subjects and was marginally significant. On the other hand, at least one episode of head trauma "severe enough to cause vertigo, dizziness, blurred or double vision, seizures or convulsions, transient memory loss, personality changes, or paralysis" occurred significantly more often prior to disease onset in patients with both young-onset and old-onset PD than in control subjects (odds ratio = 2.7). When adjusted for head trauma and rural living, smoking was inversely associated with PD, as has been previously reported (odds ratio = 0.5). There were no significant differences in early life experiences or environmental exposures between young-onset and old-onset patients. We suggest that the risk of developing PD is influenced by a variety of factors. While we were unable to link specific environmental agents with PD, our study suggests that head trauma should be reassessed as a potential risk factor for PD.

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The cause of Parkinson's disease (PD) remains a mystery, yet accumulating evidence suggests that the interactions between environmental factors and age may underlie the pathogenesis of PD.[1,2] Moreover, the discovery of a parkinsonian syndrome induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)[3,4] lends further credence to the notion that an external agent (ie, toxin) can trigger the chain of metabolic reactions culminating in the death of neurons in the substantia nigra and clinical parkinsonism ("the environmental hypothesis"). This hypothesis has stimulated the evolution of prophylactic therapies to slow PD progression[5] and provided the scientific rationale to pursue epidemiologic studies in an attempt to identify potential PD risk factors. Both descriptive epidemiological surveys of PD as well as case studies have implicated well water use, rural living, pesticide and herbicide exposure, and proximity to industry as risk factors for PD.[6-8] Several investigators have noted that exposure to environmental risk factors has been more pronounced in patients with an early onset of PD[9-11] and suggested that there may be a dose-response relationship between environmental exposure and age at PD onset. Despite these observations, an environmental toxin capable of producing PD in animals or humans has never been identified, nor have epidemics of PD been reported, as might be expected if PD were the consequence of exposure to an as yet unidentified neurotoxin. We, therefore, conducted a case-control study to further characterize the epidemiology of PD by analyzing the demographic, environmental, and early life experiences of young-onset PD patients (younger than 40 years), old-onset patients (older than 60 years), and a group of age- and sex-matched control subjects.

PATIENTS, SUBJECTS, AND METHODS

Case patients were 161 individuals with PD seen at the Graduate Hospital Department of Neurology, Philadelphia, Pa, and the Department of Neurology of the University of Medicine and Dentistry of New Jersey, New Brunswick. Patients were separated into two groups based on the age at which they experienced their first symptoms: onset before age 40 years (young-onset patients) and onset during or after age 60 years (old-onset patients). The office charts of these patients were examined to exclude individuals with a diagnosis other than idiopathic PD, who were unresponsive to antiparkinsonian medication, or who had been treated with neuroleptic drugs prior to the development of parkinsonism. Patients with significant cognitive impairment were also ex-

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cluded. All eligible young-onset patients from both institutions were contacted for interviews. Old-onset patients were randomly chosen from the Graduate Hospital population.

Control subjects matched for age (within 6 years), sex, race, and participating center were selected for 149 case patients. Each case patient was asked to nominate three nonparkinsonian subjects of the same sex and race and of similar age to serve as control subjects. Relatives and spouses were not eligible to become control subjects. One control subject was randomly selected from among the individuals nominated by each case patient and was contacted for an interview. When control subjects nominated by case patients failed to meet criteria for the study and when case patients refused to nominate control subjects, the latter were selected from among patients and hospital volunteers at the Graduate Hospital. These clinic control subjects met the same criteria for eligibility as peer-nominated control subjects, and they had no history of a movement disorder.

Data regarding environmental exposures and life experiences were collected using a structured interview. Information describing lifetime residential histories included water supply and estimates of population density. Exposure to well water and rural living were evaluated as risk factors for Parkinson's disease in two ways. A person was considered exposed to these environments if the residential history recorded at least 1 year of residence where the water source was identified as "private well or spring" and "rural" by self-report. Additionally, the cumulative number of years of residence in communities specified in this way was calculated. Exposure to insecticides and herbicides was measured by self-report. Individual questions were asked regarding use of the agents within the home, in the yard or garden, and in the neighborhood, either by members of the household or by professionals. Summary variables indicate exposure either to pesticides or herbicides if any exposure was reported. Head trauma, severe enough to cause vertigo or dizziness, loss of consciousness, blurred or double vision, seizures or convulsions, memory problems, personality changes, or paralysis, was considered a head injury for purposes of this study. Detailed smoking histories were recorded, and a smoker was considered anyone who smoked at least 1 cigarette per week for a year or more.

The strength of the association of environmental exposures with PD was assessed by computation of odds ratios (OR) or as an estimate of relative risk. Statistical methods appropriate for the analysis of matched-pair data were used to calculate odds ratios, confidence intervals (CI), and tests of statistical significance.[12] For ease of interpretation, percentages of case patients and control subjects who were exposed to environmental risk factors are reported without regard for matching; however, all analyses were performed on matched pairs. Confounding variables were evaluated by the conditional logistic regression model.[13] This model was used to adjust for the influence that these variables might have on each effect of interest. Odds ratios were also computed separately within younger and older matched pairs to examine whether the pattern of risk was similar in these two groups. This pattern was also formally tested using the logistic regression model. Finally, odds ratios for differing levels of exposure were tested for dose-response trends by logistic regression.

RESULTS

The 149 matched pairs comprised 69 young-onset and 80 old-onset pairs. Of the young-onset control subjects, 40 (58%) were peer nominated and 29 (42%) were selected from the two medical centers. Twenty-three old-onset control subjects (29%) were peer nominated, and 57 (71%) were clinic control subjects. The mean age at onset of disease for younger case patients was 34.8 years, with a mean age at diagnosis of 37.4 years, whereas the mean age at onset for older case patients was 66.9 years, with a mean age at diagnosis of 67.6 years. Overall, case patients participating in this study had been treated for an average of 8.2 years (SD = 6.4). Ninety-six percent of the study sample were white, and 60.4% were male (Table 1).

Rural living was reported more often by case patients than by control subjects, although rural residence did not achieve statistical significance (OR = 1.7, 95% CI = 1.0 to 2.9). This estimate did not change after adjustment for a history of smoking and prior head injury (Table 2); it increased only slightly with adjustment for smoking, head injury, and well water exposure (OR = 1.8, 95% CI = 1.0 to 3.4), but was not statistically significant at the .05 level. Exposure to well water for 1 year or longer was reported equally by case patients and control subjects (Table 2), and it did not change appreciably after adjustment.

Insecticide and herbicide exposure showed no significant association with PD (Table 2). Eighty-seven percent of case patients and 91.3% of control subjects reported exposure to insecticides, and odds ratios with and without adjustment were not statistically significant. The prevalence of herbicide exposure

Table 1.—Demographic Characteristics of Case Patients

Variable	No.	%
Age at onset		
Young	69	46.3
Old	80	53.7
Race		
White	143	96.0
Black	6	4.0
Sex		
Male	90	60.4
Female	59	39.6
Source*		
GH	117	78.5
UMDJN	32	21.5

*GH indicates Graduate Hospital, University of Pennsylvania, Philadelphia; UMDJN, University of Medicine and Dentistry of New Jersey, New Brunswick.

Table 2.—Crude and Adjusted Odds Ratios From Matched Pair Analysis of Environmental Risk Factors for Parkinson's Disease

Variable	Case Patients, %	Control Subjects, %	Odds Ratio	95% Confidence Interval	P
Well water, ≥1 y vs never					
Unadjusted	28.2	28.9	1.1	(0.6, 1.9)	.77
Adjusted*	. . .	. . .	0.8	(0.4, 1.6)	.60
Rural living, ≥1 y vs never					
Unadjusted	45.0	35.6	1.7	(1.0, 2.9)	.06
Adjusted†	. . .	. . .	1.7	(0.9, 3.1)	.08
Insecticide, any exposure vs none					
Unadjusted	87.2	91.3	0.7	(0.3, 1.4)	.28
Adjusted*	. . .	. . .	0.5	(0.2, 1.1)	.10
Herbicide, any exposure vs none					
Unadjusted	54.4	51.7	1.1	(0.7, 1.7)	.66
Adjusted*	. . .	. . .	0.9	(0.6, 1.5)	.73
Head injury, any prior injury vs none					
Unadjusted	31.7	17.9	2.7	(1.4, 5.2)	.004
Adjusted‡	. . .	. . .	2.9	(1.5, 5.8)	.002
Smoking, ever smoked vs never					
Unadjusted	44.9	55.8	0.6	(0.4, 1.0)	.05
Adjusted§	. . .	. . .	0.5	(0.3, 0.9)	.03
Education, ≤12 y vs 13+ y					
Unadjusted	53.0	43.6	1.6	(0.9, 2.6)	.08
Adjusted*	. . .	. . .	1.3	(0.8, 2.3)	.28

*Model adjusted for history of smoking, prior head injury, and previous rural residence.
†Model adjusted for history of smoking and prior head injury.
‡Model adjusted for history of smoking and previous rural residence.
§Model adjusted for history of prior head injury and rural residence.

was lower than that of insecticides, with 54% of case patients and 52% of control subjects reporting herbicide use in lawn, garden, or neighborhood. Odds ratios for herbicide exposure were not significant, and adjustment did not appreciably alter the estimate.

Other variables considered included education, smoking, and head injury (Table 2). Twelve years or less of school, including vocational training, was reported somewhat more often by case patients than by control subjects, but the difference was not statistically significant. Smoking was less common among case patients than it was among control subjects, with an OR of 0.6 and 95% CI from 0.4 to 1.0. Adjustment did not influence the association between smoking and PD. An episode of head trauma was associated with PD. The unadjusted OR for any prior head injury compared with no head trauma was 2.7 (95% CI, 1.4 to 5.2). After adjustment, the association between head injury and PD remained highly significant, with an OR = 2.9 (95% CI, 1.5 to 5.8).

The average number of years between the age at the time of most recent head injury and age at PD onset was 19.8 years. An average of 20.7 years elapsed between the age at the time of most recent head injury and age at time of PD diagnosis. After adjusting for potential differences in the number of years at risk for case patients and control subjects, we calculated that an average of 25.0 years elapsed between the age at the time of most recent head injury for control subjects and the age at which their matched case patients developed PD symptoms.

There were no significant differences in the relationships between environmental risk factors and PD when comparing younger and older matched pairs (Table 3). Although the OR for rural living was 2.4 in older pairs and 1.2 in younger pairs, these two were not significantly different from each other. Head injury was somewhat more strongly associated with PD in younger pairs than in older; however, the difference between the two was not significant. Exposure to well water, insecticide, or herbicide; smoking history; or education of 12 years or less was not significant in any subgroup, nor were these ORs different from each other in young and old pairs.

There was no consistent pattern to cumulative measures of exposure and PD, although the trend was statistically significant for increasing risk with increasing numbers of head injuries (Table 4). Head injury as a risk factor was significantly elevated with one injury (OR = 2.7), but not more than one (OR = 1.3). However, the trend was significant ($P = .006$), and there was no statistical evidence of deviation from linearity. The OR for rural living was significant for 1 to 10 years of rural residence (OR = 2.5) only, and the test for trend was not significant. There was no evidence of a dose-response relationship with increasing levels of exposure to well water.

Table 3.—Odds Ratios Within Young-Onset and Old-Onset Matched Pairs*

	Young-Onset		Old-Onset		
Variable	Odds Ratio	95% CI	Odds Ratio	95% CI	Difference
Well water, ≥1 y vs never	0.9	(0.4, 2.1)	1.2	(0.6, 2.7)	NS
Rural living, ≥1 y vs never	1.2	(0.6, 2.5)	2.4	(1.0, 5.4)	NS
Insecticide, any exposure vs none	0.6	(0.2, 1.7)	0.8	(0.3, 2.1)	NS
Herbicide, any exposure vs none	0.9	(0.5, 1.7)	1.3	(0.7, 2.4	NS
Head injury, any prior injury vs none	3.0	(1.2, 7.6)	2.3	(0.9, 6.1)	NS
Smoking, ever smoked vs never	0.8	(0.4, 1.6)	0.5	(0.2, 1.0)	NS
Education, ≤12 y vs 13+ y	1.0	(0.5, 2.1)	2.7	(1.2, 6.2)	NS

*CI indicates confidence interval; NS, not significant.

Table 4.—Odds Ratios Shown by Differing Levels of Exposure

Variable	Odds Ratio	95% CI	*P*
Well water			
None	1.0	. . .	. . .
1-10 y	1.0	(0.5, 2.4)	.91
10+ y	0.9	(0.5, 1.7)	.79
Rural living			
None	1.0	. . .	. . .
1-10 y	2.5	(1.2, 5.3)	.02
10+ y	1.3	(0.7, 2.4)	.47
Head injury			
None	1.0	. . .	. . .
1 injury	2.7	(1.4, 5.3)	.01
2+ injuries	1.3	(0.2, 7.3)	.78

COMMENT

Environmental Risk Factors

In the present study, environmental risk factors were not associated with either young-onset or old-onset PD, although a history of rural living approached statistical significance. These findings differ from several prior studies linking PD to environmental risk factors. Barbeau and colleagues[14,15] found an increased prevalence of PD in proximity to lumber mills and vegetable farming regions. They proposed that agricultural chemicals were causally linked to PD. Lux and Kurtzke[16] noted a north-south gradient for PD in the United States and suggested that PD prevalence increases in the more industrialized northern regions. In their case-control study of PD in China, Tanner and coworkers[17] found PD to be associated with exposure to industrial chemicals, although China is more recently industrialized and exposure occurred after 1960 in most cases. In a study of nursing home residents in two Hong Kong districts, Ho et al[18] found PD to be associated with rural living, although a significant association required more than 40 years of exposure or greater than 20 years of farming. Koller and colleagues[6] also cited rural living as a risk factor for PD in their case-control study. The modest statistical difference between rural living in Koller's survey and the present study might result from our patient population that was recruited from largely urban referral centers. Exposure to herbicides and pesticides has also been cited as a risk factor for PD.[18-20] Furthermore, several studies have noted a greater exposure to rural living and well water in young-onset patients and suggested a dose-response relationship between environmental risk factors and age at PD onset.[9-11] Rajput et al,[10] however, were unable to identify a specific well-water contaminant in their study of PD in Saskatchewan. Moreover, most of the above surveys were done in primarily agricultural areas where exposure to agricultural chemicals is common.

Meador and colleagues,[21] on the other hand, studied death records in Georgia between 1979 and 1983 and noted no difference in PD prevalence between rural and urban living. Bharucha and others[22] failed to identify environmental risk factors in monozygotic twins discordant for PD, and Wong et al,[23] in their study of PD sibships, found no increase in herbicide or pesticide exposure in affected individuals. In their recent study, Koller et al[6] failed to detect a difference in herbicide, pesticide, or farming exposure between case patients and control subjects, despite the higher incidence of rural living in PD patients. Similarly, our study failed to detect significant environmental risk factors in either old-onset or young-onset PD. We found no dose-response relationships between environmental exposures and PD.

While a history of rural living has been a consistent theme in epidemiologic studies of PD, there is no known environmental toxin that accounts for a substantially increased risk for developing PD. Studies of PD brains have shown that neuronal loss is an active, ongoing process.[24,25] The observation that many patients are no longer exposed to putative environmental risk factors at the time of death suggests that an environmental factor responsible for PD would merely serve as a trigger, initiating the chain of metabolic reactions culminating in nigral cell death. Because dopamine cell loss likely begins 20 to 30 years prior to the onset of clinical manifestations,[25,26] one might suspect that patients with young-onset PD would have had a relatively early, brief exposure to the putative factor before disease onset. An alternative explanation is that massive exposure to a presumed environmental toxin with more rapid degeneration of dopamine neurons is responsible for young-onset PD. However, there is no evidence that young-onset PD differs from old-onset PD in its primary clinical manifestations or histopathologic findings.[27] It is, therefore, improbable that dose or duration of exposure to an environmental agent is directly related to the onset of PD. We suggest that understanding differences in inherent predisposition to PD will ultimately distinguish between young- and old-onset disease and more precisely define the role of environment.

Smoking

Smoking has been inversely associated with PD in numerous surveys (see review by Baron[28]). Our study also detected a lower incidence of smoking prior to disease onset in both young-onset and old-onset patients that was statistically significant when adjusted for head trauma. Several hypotheses have been suggested to explain the possible "protective effect" of smoking in PD, although a cogent, scientific explanation is still lacking. The physiologic effects of nicotine and cigarette smoke have been studied extensively. Nicotine promotes central dopamine transmission[29,30] and increases firing rates of nigral neurons.[31,32] Components of cigarette smoke have been hypothesized to induce cytochrome oxygenases[8] and neutralize the effects of free radicals generated from dopamine metabolism.[33] It has also been suggested that cigarette smoke contains substances that might compete with an exogenous compound for brain monoamine oxidase.[34] Smoking might, therefore, be a form of protection from exogenous or endogenous oxidative stress.[1]

While these are attractive possibilities, there remain problematic inconsistencies. In a study of the dose-response relationship between intensity of smoking and PD, Golbe and coworkers[35] failed to detect a correlation between any measure of smoking and PD severity. They concluded that smoking is probably not of benefit in preventing, delaying, or improving PD. Furthermore, Tanner and colleagues[17] failed to find an inverse association between smoking and PD in their survey of patients in China. They suggested that cultural differences in the role of smoking may be more important than any specific physiologic effect. Finally, Rajput et al[36] were also unable to confirm an inverse relationship between smoking and PD in their epidemiologic survey, but they did note a preclinical personality type more prone to "psychoneurosis and psychosomatic illness" in their patients with PD compared with control subjects. Some investigators have suggested that the decreased prevalence of smoking in patients with PD may, therefore, reflect a premorbid personality type, less inclined to become a habitual smoker.[35,36] Studying the effect of cigarette smoke on animal models of PD and understanding the pathophysiology of human disease will ultimately determine whether or not components of cigarette smoke have a significant physiologic effect that can explain the inconsistent epidemiologic observations.

Head Trauma

The most significant finding in our study was the high incidence of head trauma in patients with PD prior to the onset of disease. The relationship between head trauma and PD has been controversial since Parkinson's initial description of PD and his hypothesis that symptoms evolved following cervical trauma.[37] At present, there is no evidence that head trauma causes PD with Lewy body pathology (see review by Factor et al[38]). However, head trauma has been linked to PD in some epidemiologic studies[39] and, in their review of posttraumatic movement disorders, Koller and colleagues[40] suggest that "trauma can probably worsen Parkinson's disease or perhaps even make a latent process apparent." They included peripheral trauma and head trauma in their review. Factor and Weiner[41] found a greater incidence of head trauma with loss of consciousness in a group of patients with PD than in matched control subjects. They questioned the significance of their findings because of the long latency between the traumatic event and disease onset, despite compelling evidence that the pathologic process in PD begins many years prior to the onset of clinical symptoms.[25,26] We also detected a long latency between head trauma and the onset of PD.

Depigmentation of substantia nigra neurons with cell loss and neurofibrillary tangles are seen in the brains of boxers with parkinsonian features during life.[42] Furthermore, head trauma has been associated with other neurodegenerative disorders, including Alzheimer's disease[43,44] and amyotrophic lateral sclerosis.[45,46] Pathologic changes resembling Alzheimer's disease were recently detected in the brains of boxers with dementia.[47] Additionally, Rudelli and colleagues[48] described patients with a dementia secondary to head injury that was neuropathologically identical to Alzheimer's disease. These observations suggest that head injury may not only be a significant risk factor for Alzheimer's disease but that head trauma may also cause a spectrum of neuropathological changes that can evolve many years after the traumatic event(s). While our data do not suggest that an episode of significant head trauma causes Lewy body PD, they do suggest that the pathophysiologic sequelae of head trauma should be further studied. Head trauma may be one of many risk factors that combine in a predisposed individual to induce the complex and, as yet unknown, cascade of chemical and metabolic events that eventually cause nigral cell death and PD.

There are several limitations to our study. First, our study considered patients in whom the diagnosis of PD was not newly established, and risk factors identified in studies of prevalent cases may be influenced by differences in survival of subgroups with PD. However, this type of bias tends to underestimate risk factors that carry a poor prognosis and is unlikely to substantially influence the exposures measured here. Second, we measured exposure histories by self-report using a structured questionnaire, which raises the possibility of recall bias. If patients with PD are more likely to remember an exposure than are control subjects, the measured relative risk would be spuriously high. However, the long latency between head trauma and the onset of PD in case patients and the equivalent estimate for control subjects does not suggest any important differences in the recall of significant head trauma by time frame. Furthermore, we attempted to guard against this type of bias by asking questions regarding specific memorable exposures (eg, head trauma associated with "loss of consciousness") and by asking multiple questions regarding individual exposures (eg, herbicide and insecticide exposure).

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References

1. Calne DB, Langston WJ. Hypothesis: the aetiology of Parkinson's disease. *Lancet*. 1984;2:1457-1458.
2. Calne DB. Current concepts on the etiology of Parkinson's disease. *Mov Disord*. 1989;4(suppl):S11-S14.
3. Burns RS, LeWitt PA, Ebert MH, et al. The clinical syndrome of striatal dopamine deficiency: parkinsonism induced by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). *N Engl J Med*. 1985;312:1418-1421.
4. Langston JW, Ballard P, Tetrud JW, et al. Chronic parkinsonism in humans due to a product of meperidine-analog synthesis. *Science*. 1983;219:9789-9790.
5. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;213:1364-1371.
6. Koller W, Vetere-Overfield RN, Gray C, et al. Environmental risk factors in Parkinson's disease. *Neurology*. 1990;40:1218-1221.
7. Schoenberg BS. Environmental risk factors for Parkinson's disease: the epidemiologic evidence. *Can J Neurol Sci*. 1987;14:407-413.
8. Tanner CM. The role of environmental toxins in the etiology of Parkinson's disease. *Trends Neurosci*. 1989;12:49-54.
9. Koller WC, Dolezal J, Chin T, Hassanein RS, Weldon G. Environmental risk factors in Parkinson's disease. *Neurology*. 1989;39(suppl):285.
10. Rajput AH, Uitti RJ, Stern W, et al. Early onset Parkinson's disease in Saskatchewan: environmental considerations for etiology. *Can J Neurol Sci*. 1986;13:212-216.
11. Tanner CM, Chen B, Wang W-Z, et al. Environmental factors in the etiology of Parkinson's disease. *Can J Neurol Sci*. 1987;14:419-423.
12. Kelsey JL, Thompson WD, Evans AS. *Methods in Observational Epidemiology*. New York, NY: Oxford University Press; 1986.
13. Breslow NE, Day NE. *The Analysis of Case-Control Studies*. Lyons, France: International Agency for Research on Cancer: 1980;1. Statistical Methods in Cancer Research.
14. Barbeau A, Roy M, Bernier G, et al. Ecogenetics of Parkinson's disease: prevalence and environmental aspects in rural areas. *Can J Neurol Sci*. 1987;14:36-41.
15. Barbeau A, Roy M, Cloutier T, et al. Environmental and genetic factors in aetiology of Parkinson's disease. *Adv Neurol*. 1986;45:299-306.
16. Lux WE, Kurtzke JF. Is Parkinson's disease acquired? Evidence from a geographic comparison with multiple sclerosis. *Neurology*. 1987;37:467-471.
17. Tanner CM, Chen B, Wang W-Z, et al. Environmental factors and Parkinson's disease: a case-control study in China. *Neurology*. 1989;39:660-664.
18. Ho SC, Woo J, Lee C-M. Epidemiologic study of Parkinson's disease in Hong Kong. *Neurology*. 1989;39:1314-1318.
19. Rajput AH, Uitti RJ, Stern W, et al. Geography, drinking water chemistry, pesticides and herbicides and the etiology of Parkinson's disease. *Can J Neurol Sci*. 1987;14:414-418.
20. Rajput AH, Vitti RJ. Paraquat and Parkinson's disease. *Neurology*. 1987;33:1820.
21. Meador KJ, Meador MP, Loring DS, et al. Neuroepidemiology of Parkinson's disease. *Neurology*. 1987;37(suppl 1):120.
22. Bharucha NE, Stokes LS, Schoenberg BS, et al. A case-control study of twin pairs discordant for Parkinson's disease: a search for environmental risk factors. *Neurology*. 1986;36:284-288.
23. Wong G, Gray C, Koller W. Environmental factors in siblings with Parkinson's disease. *Ann Neurol*. 1989;26:162.
24. McGeer P, Itagaki S, Akiyama H, McGeer E. Rate of cell death in parkinsonism indicates active neuropathological process. *Ann Neurol*. 1988;24:574-576.
25. Scherman D, Desnos C, Darchen F, et al. Striatal dopamine deficiency in Parkinson's disease: role of aging. *Ann Neurol*. 1989;26:551-557.
26. Riederer P, Wuketich S. Time course of nigrostriatal degeneration in Parkinson's disease. *J Neurol Transm*. 1976;38:277-301.
27. Gibb WRG, Lees AJ. A comparison of clinical and pathological features of young- and old-onset Parkinson's disease. *Neurology*. 1988;38:1402-1406.
28. Baron JA. Cigarette smoking and Parkinson's disease. *Neurology*. 1986;36:1490-1496.
29. Aceto MD, Martin BR. Central actions of nicotine. *Med Res Rev*. 1982;2:43-62.
30. Balfour DJK. The effects of nicotine on brain neurotransmitter systems. In: Balfour DJK, ed. *Nicotine and the Tobacco Smoking Habit*. Oxford, England: Pergamon Press; 1984.
31. Lichtensteiger W, Hefti F, Felix D, et al. Stimulation of nigrostriatal dopamine neurones by nicotine. *Neuropharmacology*. 1982;21:963-968.
32. Clarke PBS, Hommer DW, Pert A, Skirboll LR. Electrophysiological actions of nicotine on substantia nigra single units. *Br J Pharmacol*. 1985;85:827-835.
33. Calne DB. Current views of Parkinson's disease. *Can J Neurol Sci*. 1983;10:11-15.
34. Testa B, Naylor R, Costall B, Jenner P, Marsden CD. Does an endogenous methylpyridinium analogue cause Parkinson's disease? *J Pharm Pharmacol*. 1985;37:679-680.
35. Golbe LI, Cody RA, Duvoisin RC. Smoking and Parkinson's disease: search for a dose-response relationship. *Arch Neurol*. 1986;43:774-778.
36. Rajput AH, Offord KP, Beard CM, Kurland LT. A case-control study of smoking habits, dementia, and other illnesses in idiopathic Parkinson's disease. *Neurology*. 1987;37:226-232.
37. Parkinson J. *Essay on the Shaking Palsy*. London, England: Whittingham and Rowland, for Sherwood, Neely and Jones; 1817.
38. Factor SA, Sanchez-Ramos J, Weiner WJ. Trauma as an etiology of parkinsonism: a historical review of the concept. *Mov Disord*. 1988;3:30-36.
39. Ward CD, Duvoisin RC, Luce SE, et al. Parkinson's disease in 65 pairs of twins and a set of quadruplets. *Neurology*. 1983;33:815-824.
40. Koller WC, Wong GF, Lang A. Post-traumatic movement disorders: review. *Mov Disord*. 1989;4:20-36.
41. Factor SA, Weiner WJ. Head trauma and Parkinson's disease. *Mov Disord*. 1990;5(suppl):13.
42. Corsellis J, Burton C, Freeman-Browne D. The aftermath of boxing. *Psychol Med*. 1973;3:270-303.
43. Amaduci LA, Fratiglioni L, Rocca WA, et al. Risk factors for Alzheimer's disease (AD): a case-control study on an Italian population. *Neurology*. 1986;36:209-211.
44. French LR, Schuman LM, Mortimer JA, et al. A case-control study of dementia of the Alzheimer type. *Am J Epidemiol*. 1985;121:414-421.
45. Gallagher JP, Sanders M. Trauma and amyotrophic lateral sclerosis: a report of 78 patients. *Acta Neurol Scand*. 1987;75:145-150.
46. Sienko DG, Davis JP, Taylor JA, Brooks BR. Amyotrophic lateral sclerosis: a case-control study following detection of a cluster in a small Wisconsin community. *Arch Neurol*. 1990;47:38-41.
47. Roberts GW, Allsop D, Bruton C. The occult aftermath of boxing. *J Neurol Neurosurg Psychiatry*. 1990;53:373-378.
48. Rudelli R, Strom JO, Welch PT, et al. Posttraumatic premature Alzheimer's disease: neuropathologic findings and pathogenetic considerations. *Arch Neurol*. 1982;39:570-575.

Clinical and Genetic Analysis of Progressive Dystonia With Diurnal Variation

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• **We examined 17 patients with progressive dystonia with diurnal variation, a dominantly inherited, generalized dystonia that begins in childhood. Dystonia was typically least severe in the morning, increased as the day continued, and markedly improved with low doses of carbidopa-levodopa. We also studied the patient's parents, children, and siblings from seven families. We observed a spectrum of neurologic involvement, phenotypic variability among siblings, and incomplete genetic penetrance. Progression of motor impairment over several years, which reaches a plateau during late adolescence, is useful in distinguishing progressive dystonia with diurnal variation from cerebral palsy and degenerative disorders. It is important to recognize the subtle, as well the extreme, manifestations of progressive dystonia with diurnal variation because it is treatable. Genetic counseling must consider that mildly affected parents with little or no disability may have profoundly affected children. Appreciation of the phenotypic variability and degree of genetic penetrance will permit detailed genetic and biochemical analyses.**

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Progressive dystonia with diurnal variation (PDDV) (Segawa's dystonia)[1] is a dominantly inherited, generalized dystonia[2] that begins in childhood, usually fluctuates during the day, and dramatically improves with low doses of carbidopa-levodopa. Because of inadequate recognition, this treatable condition may be misdiagnosed as cerebral palsy, familial spastic paraparesis, or psychogenic disturbance. Without treatment, PDDV may be disabling. We analyzed the clinical course of 17 patients with PDDV, as well as their parents, children, and siblings from seven families to appreciate the clinical spectrum of this disorder.

PATIENTS AND METHODS

We studied 17 patients (five male and 12 female) with PDDV and their parents, progeny, and unaffected siblings between July 1984 and December 1989. Informed consent was obtained from the adult subjects and the parents of minor patients. We made the initial diagnosis of PDDV in 12 patients. In five patients diagnosis was established previously. Patients' ages ranged from 4 to 45 years at the time of our initial examination. Progressive dystonia with diurnal variation was diagnosed on the basis of primary, generalized dystonia that began in childhood, exhibited diurnal fluctuations, and improved with low doses of carbidopa-levodopa. The criterion of diurnal fluctuations was not used in three patients whose first-degree relatives had typical fluctuations. Two mildly affected patients are untreated and one patient is treated with trihexiphenidyl. The diagnosis of PDDV in patient 6, who died before our evaluation, was made after we examined and treated similarly affected siblings and reviewed his medical records and videotape recordings. One patient, who was previously evaluated at the National Institutes of Health, Bethesda, Md, was interviewed by telephone, but was not reexamined.

RESULTS

Laboratory Findings

The results of routine laboratory tests on 14 patients, incuding complete blood cell count, serum copper, ceruloplasmin, amino acid analysis, and electrolytes, were normal. Cranial magnetic resonance imaging and/or computed tomographic scans (in 14 patients) were normal. Reduced concentrations of homovanillic acid and biopterin in cerebrospinal fluid (in patients 4, 5, 10, and 11)[3] and tetrahydrobiopterin (BH_4) administration (in patients 4, 5, 10, 13, and 14 through 15)[4,5] have been reported previously.

Onset, Progression, and Distribution of Dystonia

The clinical characteristics of our patients with PDDV are summarized in

Family-Patient No.	Age, y†/Sex	Age at Onset, y	Dystonia Progression (Age, y‡)
I-1	45/F	8	Yes (8-14)
I-2	27/F	12	No
I-3	11/M	1.5	Yes (1.5-2)
I-4	8/M	1.5	Yes (1.5-3)
I-5	11/M	1	Yes (1-2)
II-6	12/F	2	Yes (5-11)§
III-7	7/F	5	Yes (5-7)§
IV-8	7/M	1.5	Yes (1.5-5)
IV-9	4/M	~2	No
V-10	30/F	~3	Yes (6-16)
V-11	34/F	~3	Yes (6-15)
V-12	11/F	9	Yes (9-11)§
VI-13	30/F	11	Yes (11-14)
VI-14	34/F	9	Yes (9-15)
VI-15	27/F	7	Yes (7-14)
VI-16	32/F	7	Yes (7-13)
VII-17	14/F	7	Yes (7-12)§

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the Table. Prenatal and perinatal periods and early developmental milestones were normal in all patients. Difficulty walking due to pes equinovarus, noted at 1.5 to 11 years of age (mean age, 6 years), was the initial symptom in each patient. In the majority of patients, dystonia began as a progressively worsening condition. In three patients (patients 6, 10, and 11), however, worsening of symptoms did not begin until several years after the initial appearance of dystonia. The period of progression lasted 3 to 11 years (mean, 7 years). Dystonia remained relatively constant thereafter. None of seven adults had worsening of dystonia after age 15 years. Thus far, dystonia has been nonprogressive in one mildly affected child and one adult (ages 5 and 27 years, respectively). In 15 patients, however, dystonia increased in the initially affected region and spread to the contralateral lower extremity, pelvis (11 patients), trunk (seven patients), upper extremities (12 patients), and neck (10 patients). Jaw and facial involvement (six patients) was generally asymptomatic (five patients). Speech and swallowing were involved in two brothers. The natural history of the disorder was partially obscured in four children because carbidopa-levodopa was prescribed before progression had spontaneously abated.

Neurologic deficits were limited to pyramidal and extrapyramidal systems. On examination, dystonia was generalized, affected the lower extremities most severely, and increased with action in all patients. It was symmetric in three patients and asymmetric in 14 patients, with moderate to marked asymmetry in seven of them. At least mild corticospinal tract dysfunction (velocity-dependent spasticity and hyperreflexia) was present in 12 of 16 patients examined. In six patients, spasticity was moderate to marked and equaled the degree of dystonia. Extensor plantar responses (11 patients) often disappeared with carbidopa-levodopa therapy (at least five patients). Myoclonic dystonia was present in two brothers.

Diurnal Fluctuation

Fourteen patients had diurnal fluctuation of motor performance due to increased dystonia and spasticity. These fluctuations differed from gradual, fatigue-related worsening seen in many disorders, because symptoms worsened at approximately the same time each day. Fluctuations were of variable intensity, sometimes representing the difference between ambulation and nonambulation (four patients). The fluctuation rate also varied. In 10 patients, improved motor function lasted 1 to 4 hours after awakening and reached a nadir around 10 AM to 12:00 noon. In four patients, however, it lasted only 30 to 45 minutes after awakening each morning, and two of these patients were ambulatory only during this interval. Improvement following an afternoon nap was typical, but not as pronounced as that seen in the morning. Diurnal fluctuations were absent in three mildly affected patients whose severely affected siblings (of one patient) or parents (of two patients) had typical diurnal fluctuations.

Therapy

Fourteen patients were treated with levodopa (0.7 to 2.9 mg/kg per day) and carbidopa (0.2 to 0.7 mg/kg per day) and have experienced marked clinical improvement. There has been no appearance of tolerance in 6 months to 13 years (mean, 5 years) of treatment. One patient, unable to tolerate carbidopa-levodopa because of nausea, has benefited from trihexyphenidyl (10 to 50 mg/d) for more than 10 years. Two mildly affected patients (patient 2, age 27 years, and patient 10, age 5 years) are currently untreated.

Adverse effects of carbidopa-levodopa therapy were frequent and included nausea (11 patients); choreoathetosis (three patients); behavorial hyperactivity and attention deficit disorder (two patients); insomnia, paranoia, and depression (one patient); and hypomania (one patient). These side effects were reversible with dosage reduction.

Genetic Analysis

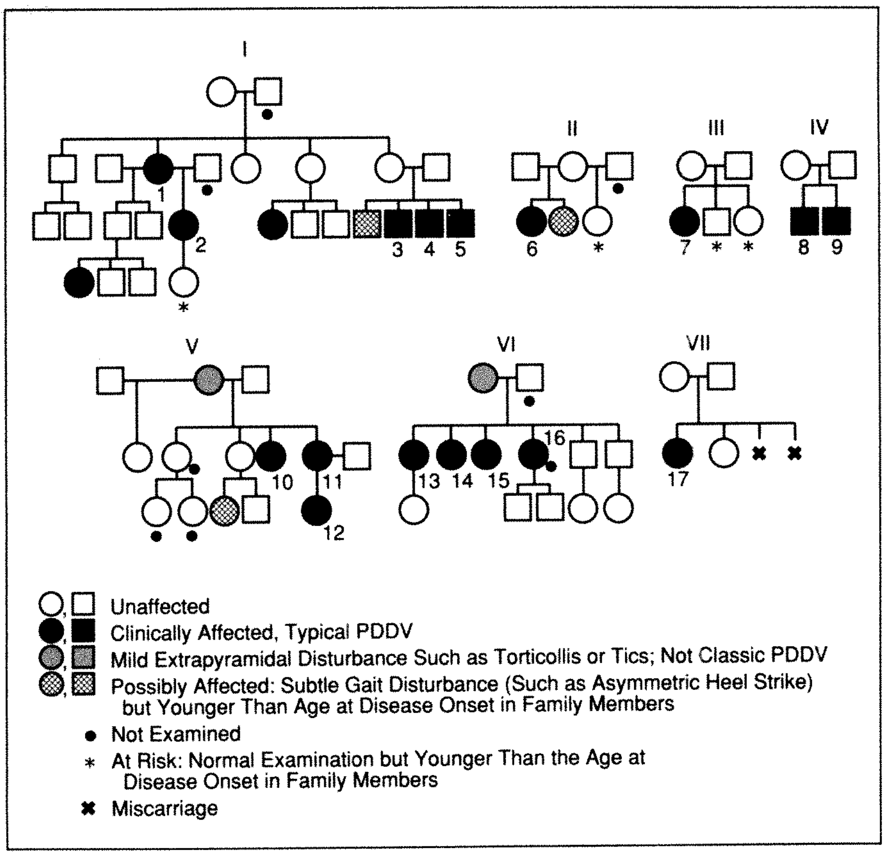
The families were of nonconsanguineous, non-Jewish, northern European ancestry (Swedish/Norwegian, German/Norwegian, English/Irish, English-French/German, American Indian-Irish/Swedish-Polish, English-Irish/Norwegian, English/English-Dutch).

The pedigrees of these families are shown in the Figure. We examined 17 of 20 parents and obtained information

Clinical Analysis of Progressive Dystonia With Diurnal Variation[*]

Dystonia Distribution									Extensor Plantar Response			
Legs and Ankles	Pelvis	Trunk	Neck	Arms and Hands	Blinking	Lower Face	Speech	Spasticity and Hyperreflexia[‡]	Pretreatment	Treatment	Asymmetry of Dystonia Pretreatment	Functional Impairment Pretreatment
+S	+S	–	–	+S	–	–	–	Moderate[‖]	–	–	Moderate	Moderate
+E	–	+S	–	–	–	–	–	None[‖]	–	NT	Mild	None
+S	+S	+S	+S	+S	+E	+E	+S	Marked[‖]	+	+	Symmetric	Marked
+S	+S	–	+S	+S	+E	+E	–	Marked[‖]	+	+	Symmetric	Marked
+S	+S	+S	+S	+S	+E	+E	+S	Marked[‖]	+	NT	Symmetric	Marked
+S	+S	–	+S	+S	–	–	–	Mild[‖]	+	–	Moderate	Moderate
+S	+S	+S	+S	+S	–	–	–	Mild[‖]	+	–	Mild	Marked
+S	+S	+S	+S	+S	+E	+E	–	Marked[‖]	+	+	Moderate	Marked
+E	–	–	–	+E	–	–	–	None[‖]	+	NT	Mild	None
+S	+S	+S	+S	+S	+E	–	–	Mild[‖]	–	–	Mild	Marked
+S	+S	–	–	+S	–	–	–	Moderate[‖]	+	–	Moderate	Marked
+S	–	–	–	+E	–	–	–	Mild[‖]	–	–	Moderate	Mild
+S	+S	+S	–	–	–	–	–	None[¶]	NE	–	Marked	Marked
+S	–	–	+S	+S	–	+S	–	Mild[‖]	+	–	Mild	Moderate
+S	–	–	+S	+S	–	–	–	None[¶]	NE	+	Mild	Marked
+S	–	+S	–	–	–	–	–	NE	NE	NE	Mild	Mild
+S	+S	–	+S	+S	–	–	–	Mild[‖]	+	–	Moderate	Moderate

[*] Plus sign indicates present; minus sign, absent; E, clinically evident; S, symptomatic; NT, no treatment; and NE, not examined.
[†] Age at last clinical evaluation.
[‡] Age during progression of symptoms.
[§] Carbidopa-levodopa was prescribed before dystonia progression had spontaneously abated.
[‖] Without medication.
[¶] With medication.


I
II
III
IV
V
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VII
1
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3 4 5
6 *
7 * *
8 9
*
10
11
12
13 14 15
16
17
Unaffected
Clinically Affected, Typical PDDV
Mild Extrapyramidal Disturbance Such as Torticollis or Tics; Not Classic PDDV
Possibly Affected: Subtle Gait Disturbance (Such as Asymmetric Heel Strike) but Younger Than Age at Disease Onset in Family Members
Not Examined
At Risk: Normal Examination but Younger Than the Age at Disease Onset in Family Members
Miscarriage

Pedigree analysis of progressive dystonia with diurnal variation (PDDV).

about unavailable (one) and deceased (two) parents. Four of the 20 parents (20%), all women, had extrapyramidal disturbance, including typical PDDV (two parents), blepharospasm and oral-facial dyskinesia (one parent), and torticollis and blepharospasm (one parent). Two parents were more severely affected (moderate to marked disability) than were their children (no disability or mild disability). Two parents had only mild symptoms (no disability) yet had children with marked dystonia, requring wheelchair use.

Five individuals (all women) with PDDV or mild disturbance of the extrapyramidal system had a total of 15 children, of which eight (53%) had PDDV. Although neurologically normal, several children (less than 5 years of age) are considered at risk for developing PDDV, because they are younger than the presenting age of their family members. Spontaneous abortion was reported by only one patient.

The patients' siblings (13 full and four half siblings) were evaluated by physical examination (16 siblings) or telephone contact (one sibling) and found to be unaffected. Thus, 17 (50%) of 34 siblings (full and half) had PDDV. Although involvement among siblings was generally similar, there was marked heterogeneity in one family—patient 8 had severe dystonia and was not ambulatory while his brother (patient 9) had only mild foot dystonia that did not require treatment.

COMMENT

Progressive dystonia with diurnal duration is an important and treatable disorder that should be considered in children and adults presenting with gait disturbance. It is readily diagnosable in patients with childhood-onset dystonia that fluctuates during the day and progresses over several years, particularly when there are similarly affected family members. Clinical suspicion and a trial of carbidopa-levodopa should not depend on a typical family history and diurnal fluctuations, however. There may not be similarly affected family members because of incomplete genetic penetrance and phenotypic variability. Diurnal fluctuations may be subtle, absent, or unrecognized if they occur rapidly or early in the morning. Progressive dystonia with diurnal duration should also be considered in patients with marked, generalized spasticity and only mild dystonia. It is essential to ask about similarly or even subtly affected family members and whether motor performance is significantly better (even for only 30 to 60 minutes) early in the morning or following an afternoon nap. Demonstration of reduced biopterin concentration in cerebrospinal fluid, although useful in confirming the clinical diagnosis, is not specific for PDDV. Decreased BH^4 has been reported[6] in Parkinson's disease, Shy-Drager's syndrome, and Steele-Richardson-Olszewski syndrome and might be expected in other degenerative conditions associated with a decreased number of BH^4-containing catecholamine or serotonin neurons.

The absence of cognitive impairment (Hallervorden-Spatz disease),[7] organomegaly and vertical gaze disturbance (Niemann-Pick disease type C),[8] aminoaciduria (biopterin synthetase deficiency[9] and glutaric acidemia[7]), and Kayser-Fleisher rings (Wilson's disease) helps exclude degenerative conditions associated with dystonia. Pigmentary retinopathy, similar to that occurring in neuronal ceroid lipofuscinosis, has been reported in a family with PDDV.[10] Onset of dystonia (particularly focal dystonia) in adulthood[11] and continued progression in the third decade of life are more consistent with dominantly inherited or idiopathic torsion dystonia than with PDDV. However, only the response to carbidopa-levodopa can reliably distinguish these types of dystonia.

Pyramidal tract disturbance is common, may be prominent (six of our patients), and often leads to erroneous diagnoses of familial spastic paraparesis and cerebral palsy.[12,13] Normal developmental milestones, onset of symptoms after infancy, and progression of symptoms over several years distinguish PDDV from cerebral palsy. Lack of progression beyond adolescence and absence of bladder and bowel involvement distinguish PDDV from familial spastic paraparesis.

Progressive dystonia with diurnal variation is often misdiagnosed in patients and its symptoms are ascribed an emotional basis. This occurred in nearly half of our patients. This misdiagnosis may be particularly common when a child can freely walk to school or during an early morning visit to the physician's office, but is unable to walk later in the day. Psychogenic movement disorder should remain a diagnosis of exclusion and should not be considered until after a trial of carbidopa-levodopa.

Carbidopa-levodopa therapy provides rapid and sustained clinical improvement. Although clinical response is obvious within 24 to 48 hours, maximum benefit, requiring dosage optimization and physical therapy, may require 8 weeks or longer. We use the following diagnostic trial: carbidopa-levodopa (Sinemet 25/100) is initiated as a half tablet each day for 2 days and then increased to 1.5 to 2 tablets each day (in two to three divided doses) over 7 to 10 days; this dosage is maintained for 7 days, and if there is no improvement, discontinued over 7 days. Administration of carbidopa-levodopa in a double-blind, placebo-crossover manner may be useful for selected, consenting patients. Dose-related side effects are frequent, particularly when beginning therapy. Carbidopa-levodopa treatment may be delayed until adulthood and still provide long-lasting benefit. Patients unable to tolerate carbidopa-levodopa have benefited from trihexyphenidyl.

Pedigree analysis (Figure) in our patients suggests dominant mendelian inheritance because the incidence of dystonia in the children of affected parents was approximately 50%. Pseudodominant inheritance cannot be excluded, however. The high female-to-male ratio (11:6) raises possibilities of reduced viability of affected male fetuses, X-linked inheritance, sex-influenced expression, or ascertainment bias. There was no evidence of reduced fertility or frequent miscarriages to suggest reduced fetal viability. Although X-linked inheritance in our families cannot be excluded, two previous reports[1,14] have each had evidence of male-to-male transmission. If the disorder in our patients is identical to that in these other families, and not a highly similar phenocopy, it is likely that expression of PDDV is sex influenced.

Ascertainment bias could also contribute to the high female-to-male ratio. There was a trend in our study for male individuals to be affected earlier and more severely than female individuals. This was particularly true with respect to pyramidal tract disturbance. It is possible that male patients are more frequently diagnosed as having severe cerebral palsy, while female patients may remain sufficiently ambulatory to have dystonia accurately recognized.

The occurrence of spontaneous mutations and nonpaternity must be considered when estimating genetic penetrance. Spontaneous mutation cannot be excluded in families III, VII, and—possibly—II, in which neither parent is affected and in which only one child has PDDV. Nonpaternity (and possibly autosomal recessive inheritance) cannot be excluded in family IV. Among families with evidence of genetic transmission (either parents and children affected or more than one affected child per family), three (of seven) sets of parents had no evidence of extrapyramidal dysfunction. Disease penetrance is thus incomplete and estimated to be 4/7 or 57%.

Marked phenotypic variability within and between families was noted with respect to the occurrence, rate, and magnitude of diurnal fluctuations, the degree of dystonia (which varied from no disability to profound impairment), and involvement of oral-pharyngeal musculature. In general, diurnal fluctuations were less apparent in those with only mild dystonia as well as in three profoundly affected children, who only had brief periods of improved motor function each morning. The genetic and biochemical basis for phenotypic variability is not known. Clinical heterogeneity within a family is presumably related to the presence of modifying genes, whose expression ameliorates or exacerbates the tendency for dystonia. Heterogeneity between families may be related to the effect of different mutations affecting the same gene. On the other hand, we cannot exclude the possibility that different families represent phenotypically similar disorders due to mutations of different genes.

The biochemical basis of this disorder is not known. Although marked levodopa responsiveness suggests a deficiency of dopamine or dopaminergic neurons, it is also possible that levodopa compensates for another neurotransmitter disturbance. Whether BH_4 deficiency reflects decreased BH_4 synthesis, increased BH_4 catabolism, or fewer BH_4-containing neurons[15] (catecholaminergic and serotonergic) is not clear. The physiologic basis for greater occurrence (and/or greater recognition) of this disorder in female individuals is also not known. Understanding the clinical spectrum of this disorder is a prerequisite for detailed genetic and neurochemical analyses. Moreover, appreciation of the subtle and extreme manifestations of this disorder will lead to greater recognition of treatable patients.

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This manuscript is dedicated to the memory of Dr M. R. Filling-Katz.

References

1. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. *Adv Neurol.* 1976;14:215-233.
2. McKusick VA. *Mendelian Inheritance in Man.* 7th ed. Baltimore, Md: Johns Hopkins University Press; 1984:210.
3. Fink J, Barton N, Cohen W, Lovenberg W, Burns RS, Hallett M. Dystonia with marked diurnal variation associated with biopterin deficiency. *Neurology.* 1988;38:707-711.
4. Lewitt PA, Miller LP, Levine RA, et al. Tetrahydrobiopterin in dystonia: identification of abnormal metabolism and therapeutic trials. *Neurology.* 1986;36:760-764.
5. Fink JK, Ravin P, Argoff CE, et al. Tetrahydrobiopterin administration in biopterin-deficient, progressive dystonia with diurnal variation. *Neurology.* 1989;39:1393-1395.
6. Williams AC, Levine RA, Chase TN, Lovenberg W, Calne DB. CSF hydroxylase cofactor levels in some neurological diseases. *J Neurol Neurosurg Psychiatry.* 1980;43:735-738.
7. Adams RD, Lyon G. Late childhood progressive genetic encephalopathies. In: Adams RD, Lyon G, eds. *Neurology of Hereditary Metabolic Diseases in Children.* Washington, DC: Hemisphere Publishing Co; 1982:226-232
8. Fink JK, Filling-Katz MR, Sokol J, et al. The clinical spectrum of Niemann-Pick disease, type C. *Neurology.* 1989;39:1040-1049.
9. Tanaka K, Yoneda M, Nakajima T, Miyatake T, Owada M. Dihydrobiopterin synthesis defect: an adult with diurnal fluctuation of symptoms. *Neurology.* 1987;37:519-522.
10. Torelli D, Lamontanara G, Bracciolini M, Ciaravolo GA. Hereditary progressive dystonia with marked diurnal fluctuation in a family with pigmentary retinopathy. *Acta Neurol.* 1986;8:626-632.
11. Fahn S. Torsion dystonia: clinical spectrum and treatment. *Semin Neurol.* 1982;2:316-322.
12. Fink JK, Filling-Katz MR, Ravin-Macrae P, Cohen WE, Hallett M, Barton N. Treatable dystonia presenting as spastic cerebral palsy. *Pediatrics.* 1988;83:137-138.
13. Boyd K, Patterson V. Dopa-responsive dystonia: a treatable condition misdiagnosed as cerebral palsy. *BMJ.* 1989;298:1019-1020.
14. de Yebenes JG, Moskowitz C, Fahn S, Saint-Hilaire MH. Long-term treatment with levodopa in a family with autosomal dominant torsion dystonia. In: Fahn S, Marsden CD, Calne DB, eds. *Dystonia 2.* New York, NY: Raven Press; 1988;50:101-111. Advances in Neurology.
15. Gibb W, Narabayashi H, Yokochi M, Iizuka R. Additional pathological observations in juvenile onset parkinsonism with dystonia. *Neurology.* 1989;39(suppl):139.

Abnormalities of Cutaneous Blood Flow Regulation in Patients With Reflex Sympathetic Dystrophy as Measured by Laser Doppler Fluxmetry

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• The response of cutaneous blood flow to autonomic stimuli was evaluated in eight patients with clinically staged reflex sympathetic dystrophy and eight healthy control subjects. Blood flow was measured in the affected and contralateral extremities by laser Doppler fluxmetry. Five autonomic stimuli were applied to the contralateral extremity during blood flow measurement in the ipsilateral affected extremity. Affected limbs of patients with reflex sympathetic dystrophy were found to have statistically significantly increased blood flow during the Valsalva maneuver and cold pressor test, while blood flow decreased in normal controls. No significant differences were found in limb temperature or baseline blood flow between patients and controls. Reflex sympathetic dystrophy stage did not affect response to the procedures. Control subjects demonstrated a rhythmic cycling of cutaneous blood flow that was absent in patients with reflex sympathetic dystrophy. These results support a central abnormality of the sympathetic nervous system in reflex sympathetic dystrophy.

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Reflex sympathetic dystrophy (RSD) is a symptom complex characterized by pain, hyperesthesia, vasomotor instability, temperature changes, and subsequent dystrophy of the affected body part. The condition was first described by Mitchell[1-3] in 1864 and has been divided into stages.[4] Stage I (acute) consists of burning or aching pain, hyperalgesia, edema, dysthermia, and increased hair and nail growth. Stage II (dystrophic) consists of brawny edema, hyperhidrosis, livedo reticularis, cyanosis, hair loss, and hypothermia. In Stage III (atrophic) disease, the pain spreads proximally, the skin thins, vasomotor instability is prominent, fascia thickens, contractures occur, and there is atrophy of all affected tissues. Initiation of RSD is generally secondary to trauma, but many other precipitating factors have been identified.[4] Progression by stages is variable, and occasionally the condition may resolve spontaneously.[4]

Multiple theories regarding the pathogenesis of RSD have been advanced.[5-11] Due to the characteristic mottling, edema, and vasomotor changes, RSD has long been considered a manifestation of sympathetic nervous system dysfunction.[12] In support of this theory, sympathetic ganglionic blockade or sympathectomy frequently alleviates the pain and symptoms of stage I disease.[13]

The purpose of our study was to measure the cutaneous blood flow in the affected and contralateral extremities of patients with RSD in response to various maneuvers that influence autonomic tone to understand further the autonomic physiology in patients with RSD.

PATIENTS AND METHODS

The most affected extremity and the contralateral extremity (either affected or unaffected) of eight patients with various stages of RSD were studied (Table 1). In all patients, disease was staged according to established criteria.[4] The patients' mean (±SD) age was 34±7 years; seven patients were women and one was a man. One arm of each of eight normal control subjects was also studied. The normal controls consisted of five women and three men with a mean age of 27±5 years. All subjects participated in the study after first providing informed consent.

Cutaneous blood flow was measured with a laser Doppler monitor (LaserFlo BPM-403-ATSI; TSI Inc, St Paul, Minn). This unit utilizes a low-power (1.6-mW) helium-neon laser, whose light is delivered to the skin surface via a flexible fiberoptic cable and is zeroed against a white surface according to manufacturer's instructions. The return signal is converted to a measurement of blood flow, volume, or velocity in the epidermal capillary loops,[14] according to a model developed by Bonner et al.[15] The monitor's analog 0- to 2.5-V output was connected through an analog/digital converter board (DT-2801; Data Translation, Marlboro, Mass) to a microcomputer (IBM-XT; International Business Machines, Boca Raton, Fla). Digital blood flow data were collected 30 times per second, averaged, and stored.

All subjects were examined after they had voided. They practiced the Valsalva maneuver and squeezing the dynamometer (Smedley-type; Therapeutic Instruments, Clinton, NJ) in several sessions preceding the experiment. A maximum strength was recorded for each hand. All patients rested in the supine position for at least 10 minutes before the initiation of studies and remained thus throughout the study. Lights were dimmed, and noise was kept to a minimum. Blood pressure, pulse, and extremity temperatures were recorded. The laser Doppler probe was placed dorsally, proximal to the web of the second and third digits, and the hand was lightly taped to the bed. A 2-minute baseline ("long-baseline") reading was recorded. In normal controls, the laser Doppler probe was placed on the nondominant hand, and all five procedures were performed with the dominant hand.

In patients with RSD, the laser Doppler probe was first placed on the most affected extremity, and the contralateral extremity was used for the procedures. The process was then reversed, with the probe on the contralateral extremity. This extremity could be symptomatic (affected) or nonsymptomatic (unaffected) due to RSD. The most affected extremity was now used for the five procedures. In the tables, affected, unaffected, and normal refer to the extremity with the probe, not the extremity undergoing the procedures.

The five procedures in the protocol were, in the order performed: (1) hyperventilation, (2) Valsalva maneuver, (3) dynamometer static grip, (4) exercise, and (5) cold pressor test. A 30- to 60-second baseline ("short-baseline") reading was obtained immediately before each procedure. Timing marks were inserted into the data stream to indicate when the patient was instructed to begin and end each procedure. Sufficient time, usually 1 to 3 minutes, was allowed between procedures for the blood flow to return to the previous short-baseline value. Each procedure is described below:

1. *Hyperventilation:* Deep breathing was coached by one of us (M.D.B.) for maximal effort and was sustained for 30 seconds.

2. *Valsalva maneuver:* The patient exhaled a full-inspiration breath through disposable positive end-expiratory pressure valves, attaining a minimum pressure of 30 cm H_2O. Before the study, each subject practiced this exhalation so that he or she just opened the valves. Exhalation continued for 30 seconds, or as limited by breath volume.

3. *Dynamometer:* This maneuver consist-

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ed of maintaining static grip for 30 seconds at one half of the previously determined maximal strength of that hand.

4. *Exercise:* The extremity was fully flexed and extended, at the elbow or the knee, at a maximal rate for 30 seconds.

5. *Cold pressor test:* The extremity was inserted to the level of the wrist or ankle in water at 0°C for 30 seconds. It was then allowed to return to baseline temperature.

The percent change in cutaneous blood flow, $\Delta\%J$, was calculated for each procedure with the following formula: $\Delta\%J = (J_1 - J_0)/J_0 \times 100\%$, where J_1 is the average blood flow during the procedure, and J_0 is the average short-baseline blood flow. Percent change flow among the categories of extremities was compared with Student's *t* test, and corrected for multiple comparisons by the method of Tukey-Kramer.[16-18] Analysis of variance was used to evaluate interlimb temperature differences. A commercially available software package (SYSTAT; Systat Inc, Evanston, Ill) was used for all statistical analyses.

RESULTS

The age, sex, stage, site of maximal involvement, and precipitating insult of all patients with RSD are summarized in Table 1. Baseline blood flow, skin temperature, and percent change in blood flow with each procedure are summarized in Table 2 and Fig 1. *P* values for comparison of affected vs unaffected limbs, affected vs normal control limbs, and unaffected vs control limbs are listed in Table 3.

The *P* values were obtained from Student's *t* test corrected for multiple comparisons. Few patients with RSD were able to squeeze the dynamometer with their affected limb, resulting in an insufficient number of blood flow measurements in unaffected limbs for a *t* test to be performed on the results of this procedure. The comparison of affected and normal limbs in this protocol is thus Student's *t* test without the Tukey-Kramer correction.

Statistical significance at the $P \leq .05$ level was achieved for the comparison of affected vs normal limbs for the cold pressor test and Valsalva maneuver. In normal controls, blood flow decreased or remained essentially unchanged in the extremity opposite the one being stimulated during the procedure. In patients with RSD, however, blood flow generally increased in both affected and unaffected limbs. This was the case for stimuli acting through both central and peripheral pathways.

Table 1.—Data for Patients With Reflex Sympathetic Dystrophy Studied

Patient/Age, y/Sex	Stage	Site of Maximal Involvement	Precipitating Event
1/30/F	II	R leg	Arthroscopy
2/36/F	III	L arm	Intravenous catheter insertion
3/30/F	III	L leg	No insult known
4/49/M	II	L arm	Trauma to hand and surgery
5/29/F	II	R leg	L-5-S-1 laminectomy
6/35/F	II	R hand	Finger trauma
7/37/F	I	R arm	Motor-vehicle accident
8/28/F	III	R arm	Shoulder dislocation and repetitive movement

Table 2.—Mean ± SD Baseline Blood Flow, Skin Temperature, and Percent Change in Cutaneous Blood Flow in Affected, Unaffected, and Normal Limbs

Procedure	Affected	Unaffected	Normal
Baseline flow, mL/min per 100 g	1.0 ± 0.5	1.3 ± 0.5	2.3 ± 2.0
Skin temperature, °C	32.7 ± 3.4	32.2 ± 3.1	32.8 ± 4.4
Hyperventilation, %	+33 ± 49	+27 ± 35	+2 ± 17
Valsalva, %	+14 ± 32	+5 ± 49	−32 ± 34
Exercise, %	+85 ± 116	+91 ± 143	−5 ± 11
Cold pressor, %	+34 ± 57	+21 ± 37	−17 ± 14
Dynamometer, %	+2 ± 12	+0 ± . . .*	−4 ± 15

*Insufficient number of patients was available to complete procedure.

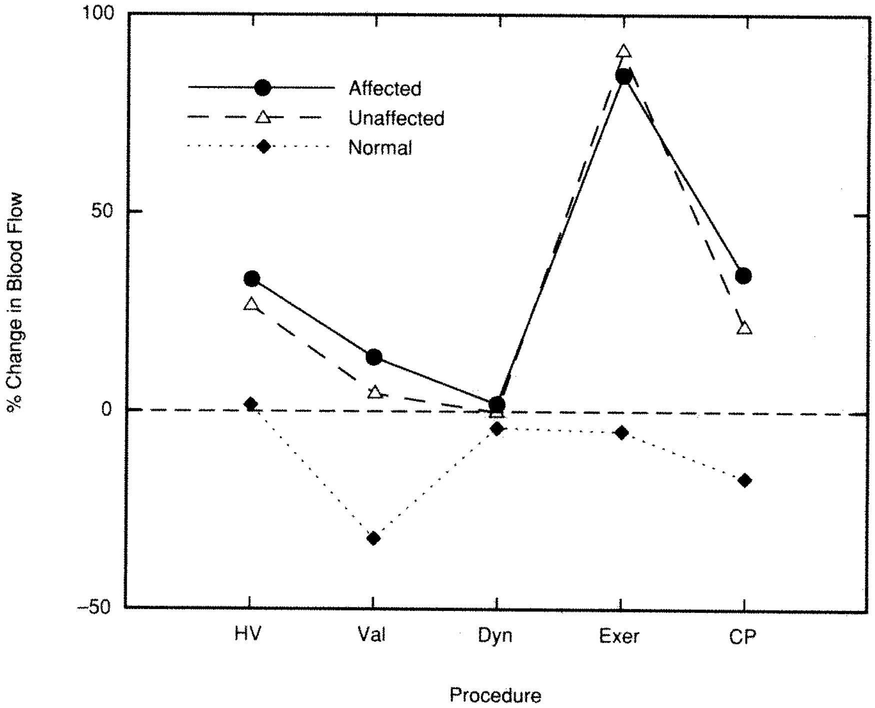

Fig 1.—Percent change in blood flow with each procedure in affected, unaffected, and normal limbs. HV indicates hyperventilation; Val, Valsalva maneuver; Dyn, dynamometer; Exer, exercise; and CP, cold pressor test.

No other comparisons were significant at this confidence level. The trend was for the unaffected limbs of patients with RSD to respond more like affected limbs rather than normal control extremities. There were no definable differences among the three groups with regard to extremity temperature ($P = .95$). Baseline cutaneous blood flow, although lower in patients with RSD, was not significantly different from that in controls ($P = .13$). Stage of RSD was not a significant factor in determining baseline blood flow ($P = .71$), response to Valsalva maneuver ($P = .98$), or response to the cold pressor test ($P = .47$).

During measurement of the short- or long-baseline blood flow, the instantaneous flow in patients with RSD in either limb was remarkably stable. In contradistinction, instantaneous blood flow of normal controls fluctuated wide-

Table 3.—Tukey-Kramer *P* Value for Pair-Wise Comparisons in Affected, Unaffected, and Normal Limbs

Procedure	Affected vs Unaffected	Affected vs Normal	Unaffected vs Normal
Initial flow	.88	.17	.36
Skin temperature	.97	.99	.93
Hyperventilation	.95	.22	.47
Valsalva	.92	.05	.19
Exercise	.99	.31	.25
Cold pressor	.86	.05	.24
Dynamometer	...*	.38†	...*

*Insufficient number of patients was available to complete procedure.
†Student's *t* value without Tukey-Kramer (only one group remains).

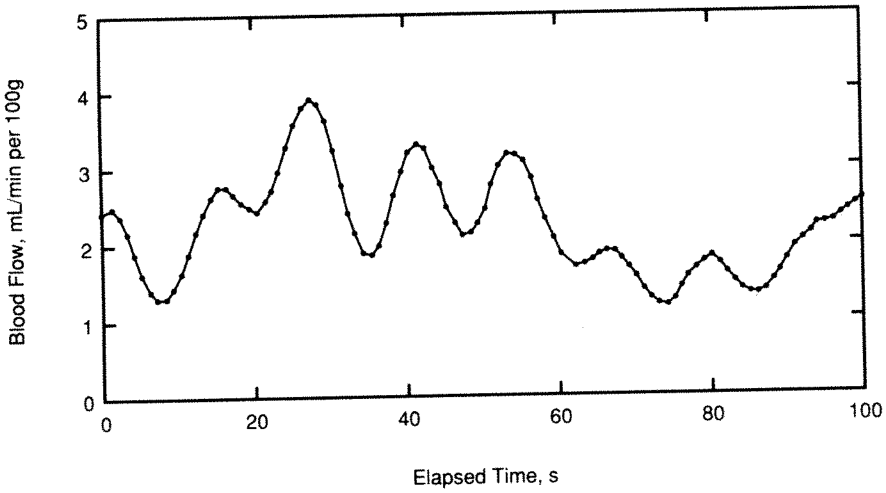

Fig 2.—Long-baseline measurement recording of blood flow over time in control subject 5.

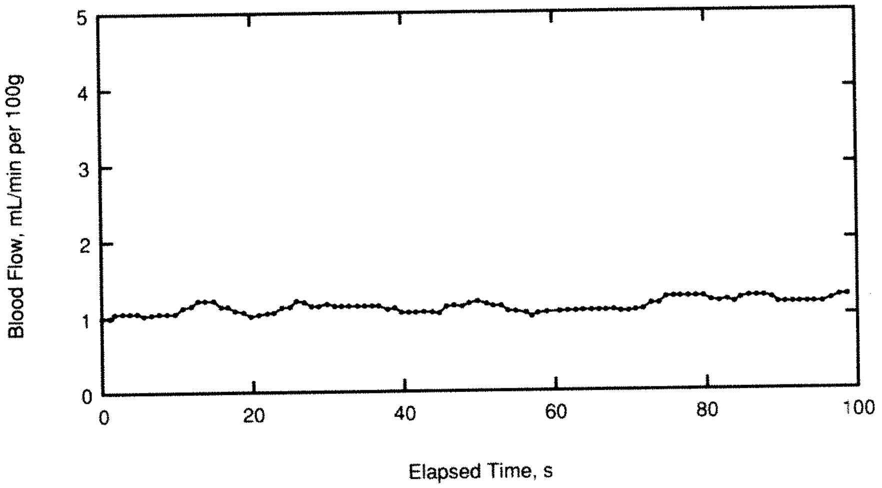

Fig 3.—Long-baseline measurement recording of blood flow over time in patient 8 with reflex sympathetic dystrophy.

ly over time in a sinusoidal pattern. As such, it was difficult to determine when rebound effects ceased and when normal-baseline blood flow began. This is best illustrated by a comparison of the long-baseline measurement of control subject 5 (Fig 2) with the long-baseline measurement of patient 8 with RSD (Fig 3).

COMMENT

Current support for the role of the sympathetic nervous system in the pathogenesis of RSD is based primarily on the relief of signs and symptoms of the disease by sympathetic denervation. In its later stages, the disease is most often sympathetically independent.[19-21] The nature of the sympathetic defect, its extent, and its sustaining mechanisms are unknown. Our study demonstrates that the defect is, at least in some aspect, central.

In our study, subjects completed five procedures that stimulate the autonomic nervous system. The Valsalva maneuver increases right atrial pressure[22] by stimulation of arterial baroreceptors and cardiac mechanoreceptors.[23] The effects of exercise and handgrip on the sympathetic system are most likely mediated by peripheral receptors in muscle.[24] Hyperventilation may also act via peripheral receptors in the muscles of respiration, but it produces a respiratory alkalosis as well, stimulating arterial chemoreceptors.[25] The cold pressor test activates sympathetic neurons in the intermediolateral column of the spinal cord.[26] Their postsynaptic sympathetic efferent fibers synapse with vasoconstrictive α and vasodilatory β_2 receptors on capacitance and resistance vessels.[27,28] Sympathetic vasodilator fibers have been identified in the forearm,[29,30] but blood flow in the hands, feet, ears, and lips has been shown to be mediated predominantly by changes in vasoconstrictor tone.[31]

Our results indicate that cutaneous blood flow responds differently to peripheral and central autonomic nervous system stimuli in patients with RSD than in normal controls. In control subjects, significant decreases in extremity blood flow were seen in the response to the Valsalva maneuver (32%) and cold pressor test (17%), which confirms the results of a prior study by Low et al.[32] Decreased blood flow in the extremities has also been described by Bannister and Mathias[33] for the Valsalva maneuver. These results also confirm those presented by Rosén et al,[34,35] who demonstrated that the cold pressor test caused a mean 37.5% blood flow decrease in controls but only a 0% to 8% drop in patients with RSD. The cold pressor and tilt tests cause an increase in plasma norepinephrine levels in normal control subjects.[36] Plasma concentration of norepinephrine under these conditions in patients with RSD is unknown.

The decreased blood flow seen during all procedures except hyperventilation suggests that blood is either pooled in the capacitance vessels of the extremity under study or is shunted to another body area. It would appear likely that exercise, handgrip, and hyperventilation would shunt blood to the exercised muscles.

The response in patients with RSD is different from that of normal controls for all five autonomic stimuli. Blood flow was invariably increased in both the affected and unaffected limbs. This finding of bilaterally increased blood flow, in conjunction with the clinical phenomenon of bilateral spread of pain, strongly suggests central involvement in RSD. A previous study demonstrated no side-to-side differences in skin temperature, blood flow, or skin conductance.[37] This can arise from a central defect that causes bilateral dysfunction of sympathetic control. We suggest that the bilateral extremity blood flow increases demonstrated in our study represent a loss of differential control of the blood supply to any one extremity, perhaps by deranged sympathetic vasoconstriction in the area of study or by abnormal sympathetic vasodilation in the resistance and capacitance vessels.[38] Under these circumstances, any central (chemoreceptive or thermoreceptive) mechanism that causes increased blood flow may well have a global effect. Our data also indicate that the "unaffected" extremity is much more likely to respond as an affected extremity, rather than as a normal control extremity.

In our study, there was no interlimb temperature difference in patients with RSD; nor was there a significant difference between these patients and controls. This is in contrast to the results of previous studies.[37] Comparison of baseline blood flow in affected, unaffected, and control limbs also reveals no statistically significant differences. This is in contrast to a study by Sylvest and others[39] in patients with RSD that demonstrated both increased resting muscle temperature and global blood flow in affected extremities. However, the "normal controls" in their study were patients with nerve injuries without clinical RSD, rather than healthy subjects. This study revealed no correlation between limb temperature and baseline cutaneous blood flow.

Vascular physiologists have long known of apparently spontaneous changes in arteriolar diameter.[40,41] These changes cause rhythmic variations in cutaneous blood flow that vary widely from individual to individual and that can be blocked by topical application of anesthetic medications.[42] Patients with RSD appear to have lost the ability to effect these variations, as evidenced by the ease in establishing a "short-baseline" readings in these patients compared with normal controls.

The effects of medications, sympathetic block, and sympathectomy were not evaluated in our study. The RSD stage was not found to significantly affect baseline blood flow or responses to the Valsalva maneuver or cold pressor test. The only newly diagnosed, untreated patient (patient 4) exhibited the most dramatic response to all stimuli. Further study of patients with each stage of RSD, before and after the performance of specific therapeutic maneuvers and the administration of medications, is needed, to differentiate the effects of therapy on central and peripheral sympathetic control of the cutaneous blood flow in patients with RSD. If a consistent pattern can be identified, a noninvasive, quantifiable test for early confirmation of RSD may be achieved.

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References

1. Mitchell SW, Morehouse GR, Keen WW. *Gunshot Wounds and Other Injuries of Nerves.* New York, NY: JB Lippincott; 1864.
2. Mitchell SW. *Injuries of Nerves and Their Consequences.* New York, NY: JB Lippincott; 1872.
3. Mitchell SW. On the disease of nerves resulting from injuries. In: Flint A, ed. *Contributions Relating to the Causation and Prevention of Disease and to Camp Diseases.* New York, NY: United States Sanitary Commission Memoirs; 1869:412-468.
4. Schwartzman RJ, McLellan TL. Reflex sympathetic dystrophy: a review. *Arch Neurol.* 1987;44:555-561.
5. Drucker WR, Hubay CA, Holden WD, Bukovnic JA. Pathogenesis of post-traumatic sympathetic dystrophy. *Am J Surg.* 1959;97:454-465.
6. Melzack R, Wall PD. Pain mechanisms: a new theory. *Science.* 1965;150:971-979.
7. Melzack R. Phantom limb pain: implications for treatment of pathologic pain. *Anesthesiology.* 1971;35:409-419.
8. Sunderland S. Pain mechanisms in causalgia. *J Neurol Neurosurg Psychiatry.* 1976;39:471-480.
9. Devor M. Nerve pathophysiology and mechanisms of pain in causalgia. *J Auton Nerv Syst.* 1983;7:371-384.
10. Thorban W. Das Sudeckische Syndrom. In: Sturm A, Birkmayer W, eds. *Klinische Pathologie des vegetativen Nervensystems.* Stuttgart, West Germany: Gustav Fischer; 1977:1186-1206.
11. Jänig W. Causalgia and reflex sympathetic dystrophy: in which way is the sympathetic nervous system involved? *Trends Neurosci.* 1985;8:471-477.
12. Leriche R. De la causalgie[,] envisagée comme une névrite du sympathique[,] et de son traitement par la dénudation et l'excision des plexus nerveux péri-artériels. *Presse Med.* 1916;24:178-180.
13. Leriche R. *La Chirurgie de la Douleur.* 3rd ed. Paris, France: Masson; 1949. [Young A, trans-ed. *The Surgery of Pain.* Baltimore, Md: Williams & Wilkins; 1939.]
14. Bonner RF, Clem TR, Bowen PD, Bowman RL. Laser-Doppler continuous real-time monitor of pulsatile and mean blood flow in tissue microcirculation. In: Chen S-H, Chu B, Nossal R, eds. *Scattering Techniques Applied to Supramolecular and Nonequilibrium Systems.* New York, NY: Plenum Press; 1981:685-701.
15. Bonner RF, Nossal R, Havlin S, Weiss GH. Model for photon migration in turbid biological media. *J Opt Soc Am A.* 1987;4:423-432.
16. Tukey JW. *Exploratory Data Analysis.* Reading, Mass.: Addison-Wesley Publishing Co; 1977.
17. Einot I, Gabriel KR. A study of the powers of several methods of multiple comparisons. *J Am Stat Assoc.* 1975;70:574-583.
18. Kramer CY. Extension of multiple range tests to group means with unequal numbers of replications. *Biometrics.* 1956;12:307-310.
19. Pak TJ, Martin GM, Magness JL, Kavanaugh GJ. Reflex sympathetic dystrophy: a review of 140 cases. *Minn Med.* 1970;53:507-512.
20. Kozin F, McCarty DJ, Sims J, Genant H. The reflex sympathetic dystrophy syndrome. *Am J Med.* 1976;60:321-331.
21. de Takáts G. Reflex dystrophy of the extremities. *Arch Surg.* 1937;34:939.
22. Vatner SF, Boettcher DH. Regulation of cardiac output by stroke volume and heart rate in conscious dogs. *Circ Res.* 1978;42:557-561.
23. Korner PI. Integrative neural cardiovascular control. *Physiol Rev.* 1971;51:312-367.
24. Hollander AP, Bouman LN. Cardiac acceleration in man elicited by a muscle-heart reflex. *J Appl Physiol.* 1975;38:272-278.
25. McQueen DS, Ritchie IM, Birrell GJ. Arterial chemoreceptor involvement in salicylate-induced hyperventilation in rats. *Br J Pharmacol.* 1989;98:413-424.
26. Covell JW. Cardiovascular control and integrated responses. In: Best CH, Taylor NB, West JB, eds. *Physiological Basis of Medical Practice.* Baltimore, Md: Williams & Wilkins; 1985:267.
27. Viveros OH, Garlick DC, Renkin EM. Sympathetic beta adrenergic vasodilatation in skeletal muscle of the dog. *Am J Physiol.* 1968;215:1218-1225.
28. Ahlquist RP. A study of the adrenotropic receptors. *Am J Physiol.* 1948;153:586-600.
29. Grant RT, Holling HE. Further observations on the vascular responses of the human limb to body warming: evidence for sympathetic vasodilator nerves in the normal subject. *Clin Sci.* 1938;3:273-285.
30. Edholm OG, Fox RH, MacPerson RK. Vasomotor control of the cutaneous blood vessels in the human forearm. *J Physiol (Lond).* 1957;139:455-465.
31. Rowell LB. Reflex control of the cutaneous vasculature. *J Invest Dermatol.* 1977;69:154-166.
32. Low PA, Neumann C, Dyck PJ, Fealey RD. Evaluation of skin vasomotor reflexes by using laser Doppler velocimetry. *Mayo Clin Proc.* 1983;58:583-592.
33. Bannister R, Mathias R. Testing autonomic reflexes. In: Bannister R, ed. *Autonomic Failure: A Textbook of Clinical Disorders of the Autonomic Nervous System.* 2nd ed. Oxford, England: Oxford University Press; 1988:289-307.
34. Rosén L, Östergren J, Fagrell B, Stranden E. Skin microvascular circulation in the sympathetic dystrophies evaluated by videophotometric capillaroscopy and laser Doppler fluxmetry. *Eur J Clin Invest.* 1988;18:305-308.
35. Rosén L, Östergren J, Roald OK, Stranden E, Fagrell B. Bilateral involvement and the effect of sympathetic blockade on skin microcirculation in the sympathetic dystrophies. *Microvasc Res.* 1989;37:289-297.
36. Goldstein DS, Bonner RF, Zimlichman R, et al. Indices of sympathetic vascular innervation in sympathectomized patients. *J Auton Nerv Syst.* 1986;15:309-318.
37. Tahmoush AJ, Malley J, Jennings JR. Skin conductance, temperature, and blood flow in causalgia. *Neurology.* 1983;33:1483-1486.
38. Drummond PD, Finch PM. Reflex control of facial flushing during body heating in man. *Brain.* 1989;112:1351-1358.
39. Sylvest J, Jensen EM, Siggaard-Andersen J, Pedersen L. Reflex dystrophy: resting blood flow and muscle temperatures as diagnostic criteria. *Scand J Rehabil Med.* 1977;9:25-29.
40. Chambers R, Zweifach BW. The topography and function of the mesenteric capillary circulation. *Am J Anat.* 1944;75:173-205.
41. Clark ER, Clark EL. Observations on living arteriovenous anastomoses as seen in transparent chambers introduced into the rabbit's ear. *Am J Anat.* 1934;54:229-286.
42. Salerud EG, Tenland T, Nilsson GE, Öberg PÅ. Rhythmical variations in human skin blood flow. *Int J Microcirc Clin Exp.* 1983;2:91-102.

Transient Ischemic Attacks With and Without a Relevant Infarct on Computed Tomographic Scans Cannot Be Distinguished Clinically

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• We prospectively studied clinical and computed tomographic (CT) scan findings in 79 patients with a transient ischemic attack (TIA) and a relevant cerebral infarction on CT, also known as *cerebral infarction with transient signs* (*CITS*). We compared the results with those of 527 concurrent patients with TIA and without cerebral infarction and also with 646 patients with persistent neurological symptoms and a relevant infarct on CT. All patients were participating in a multicenter trial. In both groups, most infarcts were of the lacunar type. Compared with TIAs without cerebral infarction, patients with CITS slightly more often had a history of hypertension (52% vs 33%), the attacks lasted longer (>1 hour, 52% vs 34%) and disappeared more slowly (over the course of hours, 39% vs 24%), and the symptoms more frequently involved speech (61% vs 41%). Despite these small differences, the reverse—the prediction of evidence on CT of infarction on the basis of the nature or time course of symptoms—proved impossible, since in each category the majority of patients had a normal CT scan. In comparison with patients with stroke and visible infarction, patients with CITS slightly more often had abnormal speech (61% vs 45%) and had a larger number of attacks (multiple attacks, 46% vs 18%). In conclusion, we found only minor clinical differences between patients with TIA with or without a relevant infarct on CT and equally small differences between patients with CITS and patients with stroke and cerebral infarction. These clinical similarities do not exclude a difference in prognosis.

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A *transient ischemic attack* (*TIA*) is defined as an acute focal neurologic deficit lasting less than 24 hours.[1] This arbitrary time limit has proved inaccurate with regard to the integrity of brain tissue, since a proportion of patients with TIAs show a relevant cerebral infarct on computed tomographic (CT) scanning.[2-6] This condition has been called *cerebral infarction with transient signs* (CITS) by Waxman and Toole.[7] These authors have speculated that patients with CITS have a different lesion in the vascular tree than do patients with TIA and without a demonstrable infarct and that their prognosis is different. Bogousslavsky and Regli[8] initially found an association between CITS and occlusion of the carotid artery, but, in a subsequent study of 57 patients with TIA, including 16 with a cerebral infarct on CT scans, no specific underlying cause was found.[6] Others, however, found an association between carotid stenosis[9,10] or carotid plaque ulceration[11] and cerebral infarction. With regard to the time course of the attacks, patients with CITS were found to have a significantly longer duration of symptoms and a smaller number of attacks.[6]

If CITS, indeed, represents a specific subgroup of patients with a different vascular cause and prognosis, this could be confirmed by differences in main symptoms (eg, cortical symptoms such as dysphasia), time course (eg, mode of onset), and prevalence of general vascular risk factors. Therefore, we have prospectively investigated possible differences in risk factors or in clinical manifestations in three groups: patients with TIA with or without a relevant cerebral infarction on CT scans, and patients with a resolving (RIND) or nondisabling stroke and a corresponding infarct on CT.

PATIENTS AND METHODS

All patients in this study were entered into a multicenter clinical trial, the Dutch TIA trial, which aimed to investigate the protective effects of low-dose aspirin and atenolol administration in patients with a TIA or a nondisabling stroke. The background and design of the study have been described elsewhere.[12] In summary, patients with one or more cerebral ischemic attacks were randomized to receive between 30 and 300 mg of acetylsalicylic acid, and, using a factorial design, 1500 patients were also randomized to receive 50 mg of atenolol or a placebo. Patients with cerebral ischemia from causes other than artery-to-artery embolism, such as polycythemia, thrombocytosis, thrombocytemia, anemia, hypoglycemia, vasculitis, or a cardiac source of embolism, were excluded. Patients with minor strokes were eligible

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for the trial as long as they were independent in most activities of daily living (grade 3 or better on the modified Rankin scale[13]).

For the patient's history, a checklist was used on which the symptoms were recorded in plain language.[14] The list contained a number of detailed multiple-choice questions about the nature of the symptoms as well as about the time course, including the mode of onset, synchronicity of the symptoms, duration of the attack, mode of disappearance, and the number of attacks. The list also contained information on the following vascular risk factors and vascular diseases: a history of hypertension, diagnosed by the general physician or an internist, either treated or not; a history of hyperlipidemia, diagnosed by an internist, treated or not; a history of diabetes, treated with oral or subcutaneous antidiabetics; angina pectoris; history of prior myocardial infarction; past bypass surgery; intermittent claudication; cigarette smoking, further specified as 20 cigarettes per day, more or less; and an enlarged heart, defined as a cardiothoracic ratio on chest roentgenogram of more than 0.5.

Between March 1, 1986, and March 1, 1989, a total of 3150 patients were randomized into the study. In 24 patients, the diagnosis was evidently wrong at the time of randomization (for instance, cerebral tumor, intracerebral hemorrhage, or vasculitis), and these patients were excluded from the analysis. We also excluded 54 patients for whom a CT scan was not obtained and 268 patients in whom the interval between the CT scan and the neurological symptoms was less than 24 hours (233 patients) or unknown (35 patients). Of the remaining patients, we excluded 638 patients with symptoms suggesting ischemia in the posterior fossa (at least one of the following: rotatory dizziness, nausea, problems with swallowing, diplopia, imbalance, and loss of direction on moving the limbs), and 84 patients with monocular blindness.

The clinical data and CT scan findings in the remaining 2082 patients were analyzed. Six hundred six patients had suffered a TIA (symptoms completely reversible within 24 hours), 422 a RIND (symptoms lasting more than 24 hours, but completely reversed within 6 weeks), and 1054 a minor stroke (persisting symptoms or signs).

All CT scans were made at the time of entry into the study but at least 24 hours after the onset of symptoms. No follow-up scans with or without contrast media were performed. The scans were independently and blindly reviewed by at least two neurologists or by one neurologist and a neuroradiologist. In case of disagreement, a third neurologist or neuroradiologist arbitrated. Only after this were the observers given access to clinical details to assess the relevance of the CT scan abnormalities.

Cerebral infarcts were defined as well-defined radiolucent lesions and were subdivided into small deep lesions, cortical end-zone infarcts (superficial radiolucent areas, involving the cortex), and border-zone infarcts (wedge-shaped hypodensities in the boundary zone between two major cerebral arteries or between deep and superficial branches of the middle cerebral artery). Cortical end-zone infarcts were further specified as involving either the partial or complete territory of the supplying blood vessel. The size of the infarct was not measured. Small deep infarcts were further subdivided according to their location as follows: anterior limb of the internal capsule, genu, posterior limb, corona radiata, basal ganglia, thalamus, or other. The infarcts were classified as *recent* if they were hemorrhagic or showed a mass effect, as *old* if adjacent ventricles or sulci were enlarged, and as of *unknown onset* in the remaining patients. The scans were classified as showing a relevant infarct only, an irrelevant infarct only, or both relevant and irrelevant infarcts, depending on the clinical symptoms.

The data were analyzed by means of the Statistical Package for the Social Sciences and statistical software (Epistat). Yates' corrected χ^2 test was used where appropriate. Comparisons between the groups were expressed as odds ratios (ORs) (the ratio of TIA with infarct to TIA without infarct, and the ratio of TIA with infarct to stroke with infarct) with the corresponding 95% confidence intervals (CIs).[15] A level of $P<.05$ was considered statistically significant.

Table 1.—Presence and Type of Cerebral Infarction on CT in Patients With CITS or Patients With Stroke*

CT Finding	TIA (n = 606) n	(%)	Stroke (n = 1476) n	(%)	P†
Relevant infarct	79	(13)	663	(45)	<<.01
Small deep	46	(58)	443	(67)	
Cortical endzone	25	(32)	174	(26)	.11
Border zone	8	(10)	46	(7)	

*CT indicates computed tomography; CITS, cerebral infarction with transient signs; and TIA, transient ischemic attack.

†Results from χ^2 test.

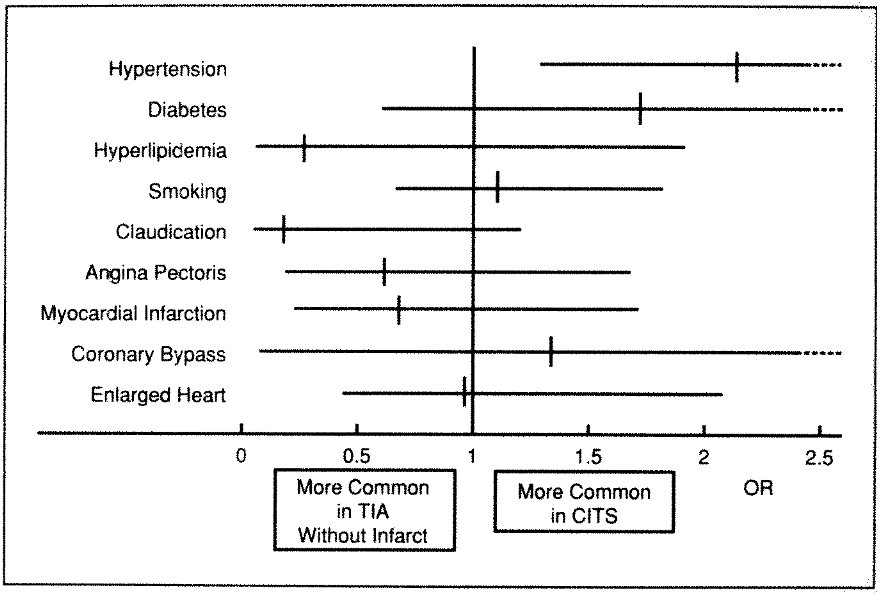

Fig 1.—Vascular risk factors and vascular disease in cerebral infarction with transient signs (CITS) and transient ischemic attacks (TIAs) without cerebral infarction. OR indicates odds ratio. The horizontal lines represent 95% confidence limits.

RESULTS

In 79 (13%) of 606 patients with TIA and 663 (45%) of 1476 patients with RIND or persisting stroke, a relevant infarct was found on CT (Table 1). No statistically significant difference was found between the two groups as far as type of infarction.

The interval between the onset of the neurologic symptoms and CT scanning was not different for patients with TIA with or without infarction ($\chi^2=7.22$, $df=5$, $P=.39$) or for patients with CITS or patients with stroke and cerebral infarction ($\chi^2=10.16$, $df=5$, $P=.07$). Only 11 patients had hemorrhagic infarcts; these were two patients with CITS and nine patients who had experienced a stroke ($\chi^2=0.10$, $df=1$, $P=.74$).

No statistically significant differences were found with regard to sex and age among TIAs without infarction, CITS, and strokes with cerebral infarction.

Table 2.—Difference in Time Course of Symptoms Between Patients With TIA and With and Without Cerebral Infarct on CT*

	TIAs					
	No Infarct (n = 527)		Infarct (n = 79)			
	n	(%)	n	(%)	P†	Proportion With Infarction in Each Category, %
Mode of onset						
1 s	293	(59)	44	(57)	.83	13
In seconds	163	(33)	25	(33)		13
1-5 min	29	(6)	7	(9)		19
6-60 min	7	(2)	1	(1)		13
Hours	2	(0)	. . .			0
All symptoms at one time	435	(86)	69	(86)	.84	14
Duration						
Seconds	12	(4)	2	(5)	.0003	14
Minutes	325	(62)	38	(43)		10
1-12 h	136	(31)	17	(43)		11
13-24 h	52	(3)	21	(9)		29
Disappearance						
Seconds	127	(24)	18	(23)	.02	12
1-5 min	139	(26)	15	(20)		10
6-60 min	130	(25)	13	(17)		9
Hours	129	(25)	31	(40)		19
Attack frequency						
1	284	(54)	43	(54)	.93	13
2-3	177	(34)	28	(35)		14
4-10	47	(9)	6	(8)		11
>10	19	(3)	2	(3)		10

*TIA indicates transient ischemic attack; CT, computed tomography.

†Results from χ^2 test.

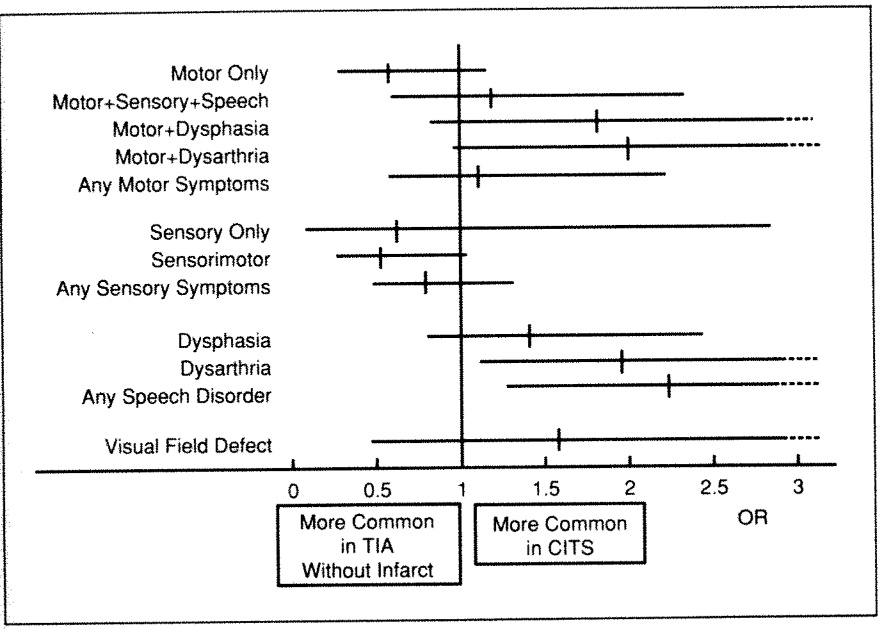

Fig 2.—Main symptom(s) in cerebral infarction with transient signs (CITS) and transient ischemic attacks (TIAs) without cerebral infarction. OR indicates odds ratio. The horizontal lines represent 95% confidence limits.

Comparisons Between Patients With TIA With or Without a Relevant Cerebral Infarct on CT

Vascular Risk Factors and Vascular Disease.—Figure 1 shows that patients with TIA and cerebral infarction more often were known to have hypertension (52% vs 33%, $P = .002$). The dotted line in the figure indicates that the upper 95% confidence limit exceeded the value of 2.5. No other significant differences between the two groups were found.

Time Course of Symptoms.—Table 2 shows the differences in time course of symptoms between patients with TIA with or without cerebral infarction. No differences were found in the mode of onset or in the number of attacks. The CITS group included more patients with attacks lasting longer than 1 hour (52% vs 34%, $P = .0003$) and, accordingly, more patients in whom the symptoms were slower to disappear (in terms of hours, 40% vs 25%; $P = .02$).

Despite this difference in time course between patients with CITS or TIA, the prediction of CT infarction on the basis of the duration of the attack proved impossible, since, in each category, the majority of patients had had a normal CT scan (Table 2).

Nature of Symptoms.—In Fig 2, the differences in main symptoms between the two groups are shown. In patients with CITS, the symptoms more often involved speech (61% vs 41%, $P = .001$), either dysarthria (difficulty in pronouncing words) (OR = 1.95; 95% CI, 1.11 to 3.42; $P = .01$) or dysphasia (difficulty in finding or understanding words) (OR = 1.39; 95% CI, 0.79 to 2.45; $P = .27$). Patients with CITS and motor symptoms more frequently described their symptom as weakness or clumsiness, whereas patients with TIA and without cerebral infarction more often complained of a "heavy" or "tired" limb (OR = 2.23; 95% CI, 0.95 to 5.48; $P = .06$). The terms used in describing visual symptoms in one hemifield (hazy, flashlights, black, or blind) did not differ significantly between the two groups.

No statistically significant differences were found in accompanying symptoms, such as headache (OR = 0.72; 95% CI, 0.33 to 1.51; $P = .45$), lightheadedness (OR = 0.81; 95% CI, 0.38 to 1.67; $P = .67$), or unconsciousness (five patients only, one of whom had an infarct on CT).

The distribution of either motor or sensory symptoms over an arm, a leg, and the face was not different between the two groups.

Comparison Between Patients With CITS and Patients With Stroke and Cerebral Infarction on CT

Vascular Risk Factors and Vascular Disease.—Figure 3 shows no differences in vascular risk factors or vascular disease between patients with CITS and patients with stroke and a demonstrable cerebral infarct.

Time Course of Symptoms.—Since the duration of the attack differed by definition between patients with CITS and patients with stroke, both the duration and rate of disappearance of symptoms were not compared. The mode of

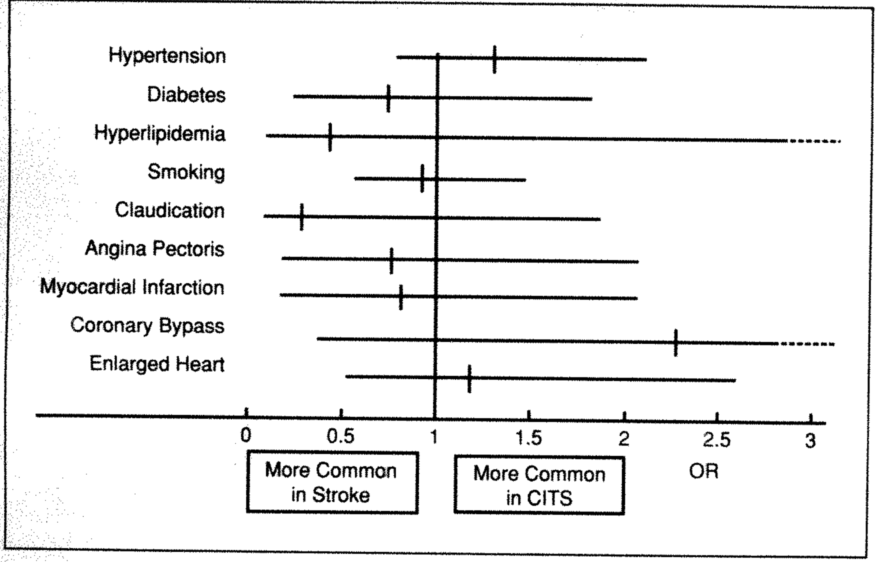

Fig 3.—Vascular risk factors and vascular disease in cerebral infarction with transient signs (CITS) and stroke with cerebral infarction. The horizontal lines represent 95% confidence limits.

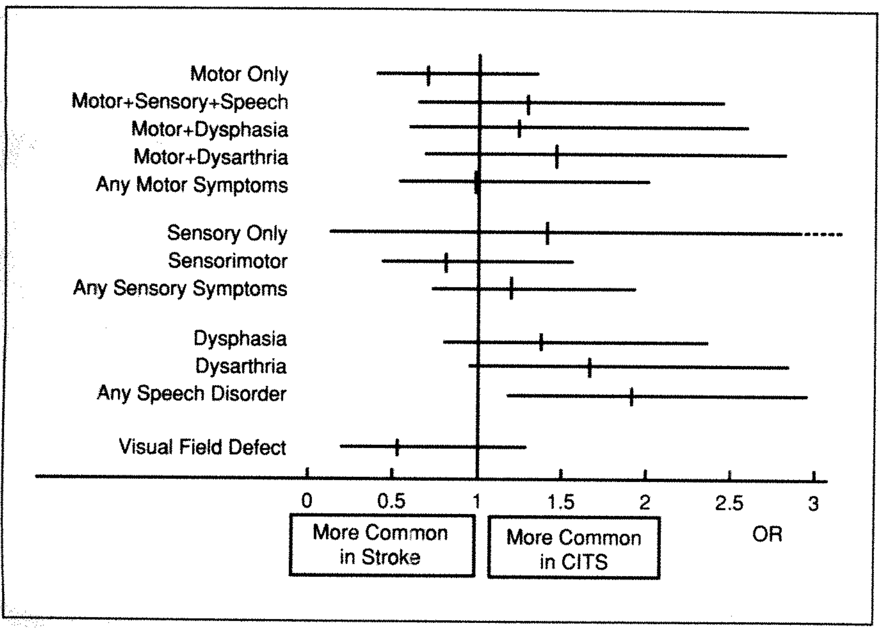

Fig 4.—Main symptom(s) in cerebral infarction with transient signs (CITS) and stroke with cerebral infarction. The horizontal lines represent 95% confidence limits.

onset was not significantly different between the two groups but tended to be slower in patients with stroke ($P=.08$). The number of attacks was significantly smaller in patients with stroke (multiple attacks, 46% vs 18%; $P<<.01$).

Nature of Symptoms.—Figure 4 shows that the differences between the two groups were very small with regard to symptoms. Patients with CITS had had a slight preponderance of speech disturbances (61% vs 45%; OR = 1.88; 95% CI, 1.14 to 3.09; $P=.01$), dysarthria in particular (OR = 1.63; 95% CI, 0.94 to 2.81; $P=.08$). No difference was found in the patients' description of visual and motor disturbances, in the distribution of motor and sensory symptoms, or in the occurrence of lightheadedness and headache as accompanying symptoms.

COMMENT

Our study shows only slight, and only a few, clinical differences between patients with TIA with or without a relevant infarct on CT. The relative preponderance of attacks exceeding 12 hours in TIAs with infarction confirms the findings of Bogousslavsky and Regli.[6] We also found a slower disappearance of symptoms in these patients, but no difference in the number of attacks. In contrast with this previous study, which showed that 84% of patients with attacks lasting more than 45 minutes had a relevant infarct on CT scans,[6] we found that the presence of cerebral infarction could not be predicted from any of the time-course variables, since in each category patients with a normal CT scan formed a large majority. The single difference in the nature of symptoms—dysarthria more often in patients with TIA and cerebral infarction—is difficult to explain and may be a chance finding. Little is known about the predictive value of individual symptoms with regard to the underlying arterial lesion or the prognosis of the patient. This issue is currently under investigation in the Dutch TIA trial.

Does CITS represent a subgroup of infarct with a specific vascular cause? This seems unlikely. First, in accordance with the findings of others,[6,11] we found that the clinical manifestations of patients with TIA with or without infarction mostly overlap. One might object that we did not perform a multivariate analysis. However, since the clinical differences that we detected in the univariate analysis were very small, the results would not have changed our ultimate conclusion. Second, others found no difference in the prevalence of cardiac emboligenic abnormalities or extracranial arterial disease between the two groups.[6] On the other hand, several investigators have reported an association between carotid stenosis[9,10] or carotid plaque ulceration[11] and cerebral infarction on CT, which suggests that CITS is associated with a more advanced degree of extracranial and intracranial arterial disease. Third, in a previous study we found no difference in the type of cerebral infarction (small deep, cortical end zone, or border zone) among patients with a TIA, RIND, or partial stroke but only in the frequency of relevant infarcts on CT.[16] Finally, newer imaging techniques such as positron emission tomography and magnetic resonance imaging may be even more sensitive than CT in documenting ischemic lesions.[17,18] Separating patients with TIA by the results of CT scanning alone therefore seems inaccurate. In addition, our study shows that the clinical differences between patients with CITS and patients with stroke and cerebral infarction were equally small, which suggests that CITS closely resembles strokes with cerebral infarction, as do TIAs without CT abnormalities.

The next step will be to investigate whether CITS represents a clinical subgroup with a specific prognosis. In the coming years, we shall analyze the outcome of events in the same cohort of patients to determine possible differences among the following four groups of patients: those with symptoms lasting less than 24 hours, those with symptoms lasting longer than that, and those with or without a relevant infarct on CT on admission.

References

1. The Ad Hoc Committee on the Classification and Outline of Cerebrovascular Disease, II. *Stroke.* 1975;6:566-616.
2. Perrone P, Candelise L, Scotti G, De Grandi D, Scialfa G. CT evaluation in patients with transient ischemic attack: correlation between clinical and angiographic findings. *Eur Neurol.* 1979;18:217-221.
3. Ladurner G, Sager WD, Iliff LD, Lechner H. A correlation of clinical findings and CT in ischemic cerebrovascular disease. *Eur Neurol.* 1979;18:281-288.
4. Donnan G, Tress BM, Bladin PF. A prospective study of lacunar infarction using computed tomography. *Neurology.* 1982;32:49-56.
5. Calandre L, Gomara S, Bermejo F, Millan JM, Del Prozo G. Clinical CT correlations in TIA, RIND, and strokes with minimum residuum. *Stroke.* 1984;15:663-666.
6. Bogousslavsky J, Regli F. Cerebral infarct in apparent transient ischemic attack. *Neurology.* 1985;35:1501-1503.
7. Waxman SG, Toole JF. Temporal profile resembling TIA in the setting of cerebral infarction. *Stroke.* 1983;14:433-437.
8. Bogousslavsky J, Regli F. Cerebral infarction with transient signs (CITS): Do TIAs correspond to small deep infarcts in internal carotid artery occlusion? *Stroke.* 1984;15:536-539.
9. Grigg MF, Papadakis K, Nicolaides AN, et al. The significance of cerebral infarction and atrophy in patients with amaurosis fugax and transient ischemic attack in relation to internal carotid artery stenosis. *J Vasc Surg.* 1980;2:215-222.
10. Zukowski AJ, Nicolaides AN, Lewis RT, et al. The correlation between carotid plaque ulceration and cerebral infarction seen on CT scan. *J Vasc Surg.* 1984;1:782-786.
11. Murros KE, Evans GW, Toole JF, Howard G, Rose LA. Cerebral infarction in patients with transient ischemic attacks. *J Neurol.* 1989;236:182-184.
12. The Dutch TIA Study Group. The Dutch TIA Trial: protective effects of low-dose aspirin and atenolol in patients with transient ischemic attacks or non-disabling stroke. *Stroke.* 1988;19:512-517.
13. Van Swieten JC, Koudstaal PJ, Visser MC, Schouten HJA, Van Gijn J. Interobserver agreement for the assessment of handicap in stroke patients. *Stroke.* 1988;19:604-607.
14. Koudstaal PJ, Van Gijn J, Staal A, Duivenvoorden HJ, Gerritsma JGM, Kraaijeveld CL. Diagnosis of transient ischemic attacks: improvement of interobserver agreement by a checklist in ordinary language. *Stroke.* 1986;17:723-728.
15. Sandercock PAG. The odds ratio: a useful tool in neurosciences. *J Neurol Neurosurg Psychiatry.* 1989;52:817-820.
16. Koudstaal PJ, van Gijn J, Frenken CWGM, et al for the Dutch TIA Study Group. TIA, RIND, minor stroke: a continuum or different subgroups? *J Neurol Neurosurg Psychiatry.* In press.
17. Awad I, Modic M, Little JR, Furlan AV, Weinstein M. Focal parenchymal lesions in transient ischemic attacks: correlation of computed tomography and magnetic resonance imaging. *Stroke.* 1986;17:399-402.
18. Powers WJ, Raichle ME. Positron emission tomography and its application to the study of cerebrovascular diseases in man. *Stroke.* 1985;16:361-376.

Correction

Incorrect Data.—In the article entitled "Tuberculous Meningitis" that appeared in the December 1990 issue of the ARCHIVES (*Arch Neurol.* 1990;47:1313-1317), errors appeared in the body of Table 4 and in the footnote to that table. In the body of Table 4, in the last line under the heading "British Research Council on Admission," the following value appeared: "2.4 ± 1.7." The last line under this heading should have been left blank. In the last line under the heading "Duration of Symptoms Prior to Admission, wk," a blank space appeared. In the last line under this heading, the value of "2.4 ± 1.7" should have appeared. The first sentence to the footnote in Table 4 read as follows: "Diagnostic categories for tuberculous meningitis: seven, definite; two, probable." The sentence should have read as follows: "Diagnostic categories for tuberculous meningitis: one, definite; two, probable."

Nuclear Hemodynamic Vertebrobasilar Insufficiency

A New Approach With the Xenon Xe 133 Method

Paul Trouillas, MD; Norbert Nighoghossian, MD; Bernard Philippon, PhD

• Vertebrobasilar insufficiency is a well-known syndrome, but no corresponding hemodynamic deficit has yet been established. We propose to define nuclear hemodynamic vertebrobasilar insufficiency on the basis of an oligemia lower than 35 mL/100 g per minute in the brain stem–cerebellar region with use of the xenon Xe 133 inhalation method. Fifteen patients fulfilling this criterion underwent four-vessel angiography, computed tomography, and a standardized neurologic examination. An acetazolamide test showed poor reactivity in more than half of the patients, sometimes specifically in the vertebrobasilar area. With use of single-photon emission computed tomography and intravenous technetium Tc 99m–labeled hexamethylpropyleneamineoxime in two cases, the considerable decrease of regional cerebral blood flow in the brain stem–cerebellar region was confirmed. An excellent correlation was observed between the existence of nuclear hemodynamic vertebrobasilar insufficiency and angiographically proved arterial occlusions. The dominant nuclear oligemic zone was regularly on the side of the anatomic arterial chief lesion. Clinical manifestations included rare transient ischemic attacks (in one of 15 patients), intermittent basilar symptoms (in 15 of 15 patients), and a subacute vertebrobasilar "threatening" syndrome. Thus, imaging of a nuclear hemodynamic vertebrobasilar deficit provides an objective basis to the diagnosis of vertebrobasilar insufficiency and useful objective data for revascularization surgery.

(*Arch Neurol.* 1991;48:921-929)

The concept of vertebrobasilar insufficiency and the corresponding intermittent clinical pictures were first introduced by Denny-Brown[1,2] and Millikan and Siekert.[3]

Angiography of the vertebrobasilar system has demonstrated in vivo intracranial or extracranial arterial lesions[4,5] that are able to induce a hemodynamic deficit as first postulated by Denny-Brown.[1,2] Caplan and Rosenbaum[6] underlined the high interest about angiography to establish a topographic diagnosis of the occlusive process.

However, the existence of a real hemodynamic vertebrobasilar deficit, in the so-called clinical vertebrobasilar insufficiency syndrome, has not been demonstrated by conventional measurement of cerebral blood flow.[7]

We propose herein to identify a true posterior circulation hemodynamic deficit by defining nuclear hemodynamic vertebrobasilar insufficiency (NHVBI) as a blood flow decrease in the brain stem–cerebellar region to lower than 35 mL/100 g per minute, when blood flow is measured by the xenon Xe 133 inhalation method. This arbitrary limit was chosen because 35 mL/100 g per minute is considered a putative threshold for oligemia. In 15 patients exhibiting this hemodynamic syndrome, four-vessel angiographic findings, computed tomographic (CT) scans, and clinical data were studied. Thus, classic aspects of vertebrobasilar insufficiency were confirmed. A new clinical picture, vertebrobasilar hemodynamic "threatening" syndrome, could be observed.

PATIENTS AND METHODS

Cerebral Blood Flow Measurements

A double-headed camera (Rota camera, Siemens-France, Saint-Denis, France) equipped with two low-resolution (full width half maximum, 15 mm) and high-efficiency collimators was used to measure regional cerebral blood flow (rCBF) during a period of 2 minutes after 1.5 minutes' inhalation of ^{133}Xe. The patients were in the supine position. The inhalation gas mixture contained approximately 50 to 70 mBq/L at the first (or only) measurement, 100 to 120 mBq/L at the second measurement, and 130 to 150 mBq/L at the third measurement. Each collimator was positioned parallel to the sagittal axis of the brain. The blood flow was calculated by the method of Initial Slope Index according to Fox et al.[8] Software was designed to calculate the mean blood flow in identified oligemic areas and in standardized anatomic zones, particularly in the brain stem–cerebellar region.

Selection of Patients

The selection of patients was strictly performed on a hemodynamic basis. All kinds of neurologic patients with various symptoms underwent cerebral blood flow measurements. Patients who had had recent complete or minor strokes and who had tumors were excluded from the study. For the sake of detecting primary ischemic blood flow variations, patients with degenerative diseases and migraine were also excluded.

The definition of NHVBI was the existence of an area with an oligemia lower than 35 mL/100 g per minute in the brain stem–cerebellar region; an SD of 2.8 mL/100 g per minute, obtained from our reproductibility series, was accepted for this limit. The measurement 35 mL/100 g per minute is generally considered a possible threshold for oligemia in clinical studies,[9] although it has not yet

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been documented in experimental studies.[10] The brain stem–cerebellar region has been chosen because its vascularization is exclusively of vertebrobasilar origin, while the occipital region recorded gets some blood supply from the carotid system. Twenty-seven consecutive patients with this hemodynamic syndrome were selected.

Of this group, 15 subjects (mean age, 62.1 ± 12.6 years) gave informed consent to undergo selective four-vessel angiography (14 times by the Seldinger technique), CT, a thorough investigation of their symptoms, and a standardized neurologic examination. This series of 15 subjects is presented herein.

Moreover, 15 age- and sex-matched patients with asymptomatic unilateral or bilateral carotid stenosis, diagnosed by Doppler ultrasonography and without detectable vertebrobasilar extracranial ultrasonographic abnormality, underwent ^{133}Xe rCBF measurement. Nineteen totally healthy controls underwent the same procedure.

Table 1.—Regional Cerebral Blood Flow (rCBF) Brain Stem-Cerebellum Values in Nuclear Hemodynamic Vertebrobasilar Insufficiency (NHVBI)

	Brain Stem–Cerebellum Region rCBF measurement, mL/100 g per Minute		Cerebral Hemispheric CBF Measurement, mL/100 g per Minute	
Patients	R	L	R	L
	Pure NHVBI			
1	28.7	25.6	38.5	39.6
2	32.3	35.1	40.0	40.2
3	40.6	36.7	41.8	41.3
4	38.1	30.8	41.0	40.4
5	35.5	39.1	42.0	41.2
6	42.9	36.1	43.5	41.7
	NHVBI With Cerebral Insufficiency			
7	31.9	33.3	37.2	36.6
8	35.1	37.2	32.6	33.3
9	33.0	31.8	37.2	35.6
10	34.6	36.2	37.9	36.9
11	31.9	31.3	37.9	36.9
12	30.6	29.0	34.3	33.8
13	27.6	34.2	33.0	34.8
14	27.7	34.0	34.1	35.5
15	25.6	22.3	32.5	30.0
Mean ± SD	33.1 ± 4.9	32.9 ± 4.6	37.6 ± 36	37.3 ± 35

Rotation and Acetazolamide Tests

Additional tests were performed in 10 patients with NHVBI. A test of rotation of the head was first done. When the rotation on one side induced clinical symptoms, this side was chosen for the test. If there was no clinical indication, rotation was randomly done on the right or the left side. A rotation position at 45° was maintained for 4 minutes, and the rCBF was then measured.

After rest, the head having returned to the neutral position, 1 g of acetazolamide was injected, and the rCBF was again measured 15 minutes later to study the vasodilatory capacity of encephalic arteries.[11]

Single-Photon Emission CT and Technetium Tc 99m–Hexamethylpropyleneamineoxime (HM-PAO) Examinations in Two Patients

In cases 1 and 4, tomographic cerebral blood flow examinations were performed with the ^{99m}Tc–HM-PAO method and with a double-headed camera (Rota camera; Micro Delta calculator, Siemens-France). A dose of 555 mBq was administered; the tomographic studies were performed 10 minutes after intravenous injection. The reconstruction procedure used is the classic filtered back projection method with a Butterworth filter, on 64 × 64 matrix.

RESULTS

The Syndrome of NHVBI

Blood flow in identified oligemic areas ranged from 22.3 to 36.4 mL/100 g per minute, and the mean value of all identified oligemic zones (the right and/or the left side) was 29.2 ± 3.7 mL/100 g per minute. When the overall brain stem–cerebellar region was considered, the mean blood flow was 33.1 ± 4.9 mL/100 g per minute on the right side and 32.9 ± 4.6 mL/100 g per minute on the left side. In the group of age- and sex-matched patients with carotid stenosis, there was no oligemic area in the posterior circulation region. The mean blood flow in the brain stem–cerebellar region was 45.1 ± 6.4 mL/100 g per minute on the right side and 46.8 ± 6 mL/100 g per minute on the left side. When compared with the mean NHVBI values, the difference was statistically significant at $P<.001$ on the left side and at $P<.02$ on the right side. The lower limit in patients with carotid stenosis (mean − 2 SDs) was 32.3 mL/100 g per minute on the right side and 34.8 mL/100 g per minute on the left side. The mean brain stem–cerebellar rCBF in healthy controls was 54.3 ± 4.3 mL/100 g per minute on the right side and 52.0 ± 5.5 mL/100 g per minute on the left side.

The patients with NHVBI could be classified into two groups according to the hemispheric rCBF values (Table 1).

Pure NHVBI (n = 6).—There was a sharp contrast between normal cerebral hemispheric blood flow (>35 ± 2.8 mL/100 g per minute) and NHVBI. Pure NHVBI was bilateral (n = 2) or unilateral (n = 4).

In index case 1 (56-year-old woman, heavy smoker), this pattern of bilateral specific NHVBI appeared clearly (Figs 1 and 2), and the oligemic phenomenon was permanent (Figs 1 and 3) when rCBF measurements were repeated. The HM-PAO CT findings confirmed the decrease in rCBF in the brain stem–cerebellar region (Figs 4 and 5). In case 4, a similar but unilateral pattern was observed with ^{133}Xe (Fig 6) and confirmed with the HM-PAO technique.

Additional tests were performed in six cases (Table 2). The rotation test showed a brain stem–cerebellar blood

Fig 1.—Case 1, xenon Xe 133 study technique, examination 1. Typical pure nuclear hemodynamic vertebrobasilar insufficiency with severe oligemia (24 mL/100 g per minute) in the left-sided brain stem–cerebellar region.

Fig 2.—Case 1, examination 2. Nuclear hemodynamic vertebrobasilar insufficiency was also observed on the right side but was less marked than on the left side. This hemodynamic syndrome was already found on this side 1 year earlier. Slight oligemic areas were observed in the parietal and frontal parasagittal regions.

Fig 3.— Case 1, examination 2. The same hemodynamic syndrome was found 1 year later, in the left-sided brain stem–cerebellar region, with a slight extension to the occipital zone.

Fig 4.—Case 1. technetium Tc 99m hexamethylpropyleneamineoxime single-photon emission computed tomographic image. This technique confirmed the existence of a considerable decrease in regional cerebral blood flow in the brain stem–cerebellar region. Note the existence of oligemia in the inferior part of the temporal lobes.

Fig 5.—Case 1, technetium Tc 99m hexamethylpropyleneamineoxime single-photon emission computed tomographic image. Note the normality of hemispheric cerebral blood flow.

Fig 6.—Case 4. Unilateral nuclear hemodynamic vertebrobasilar insufficiency with a severe oligemic zone (23.8 mL/100 g per minute) close to ischemic penumbra.

Fig 7.—Case 1, examination 2. The acetazolamide test provoked an improvement of the overall right-sided brain stem–cerebellar blood flow, but there was a zone of specific vertebrobasilar nonreactivity to acetazolamide testing.

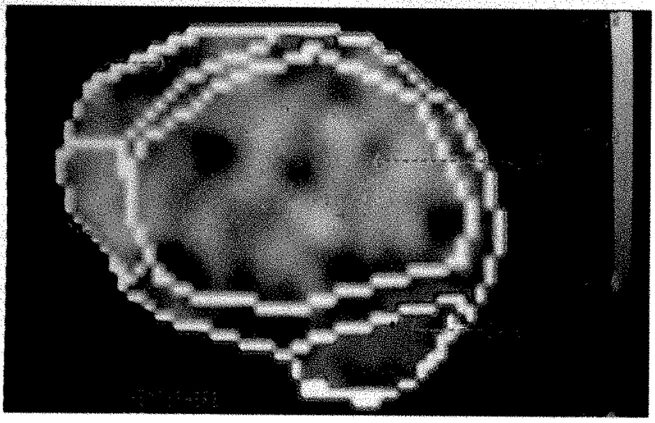
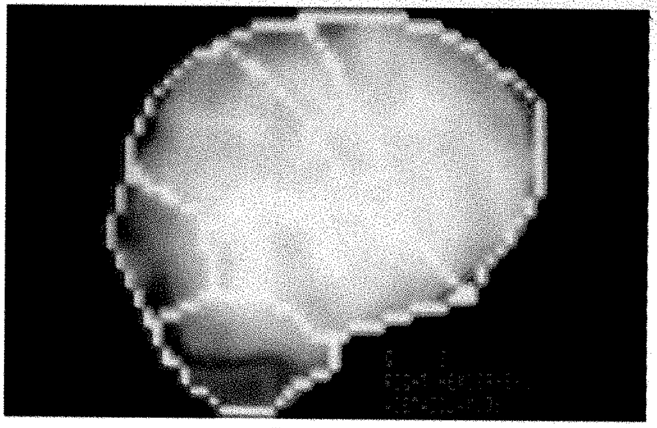


Figure 1.



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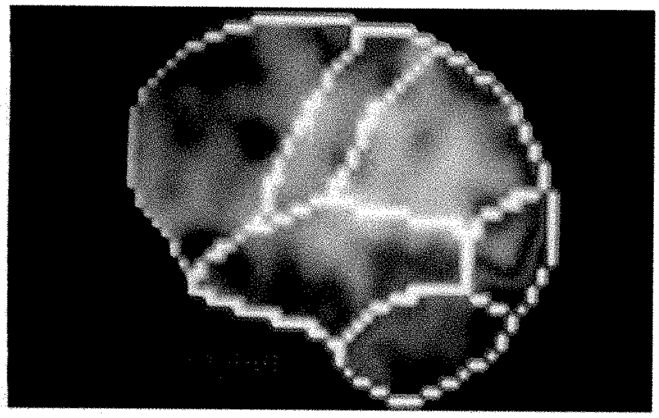

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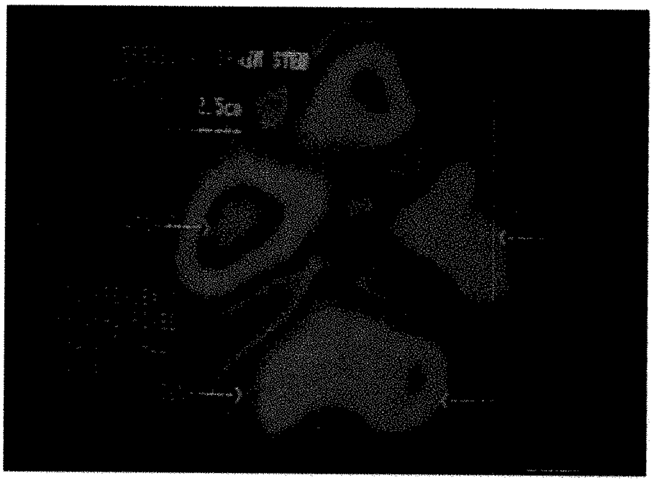

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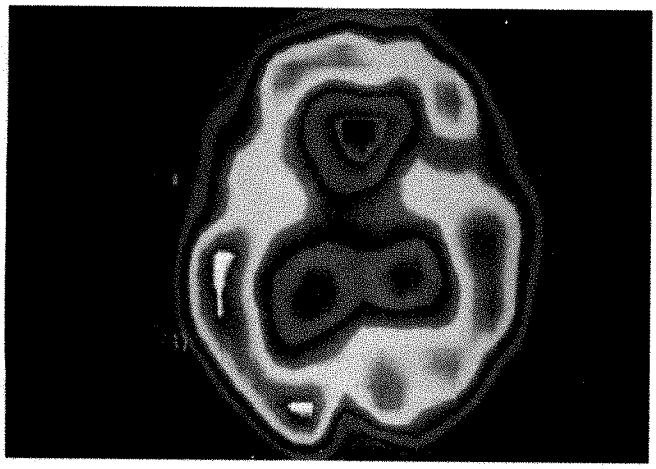

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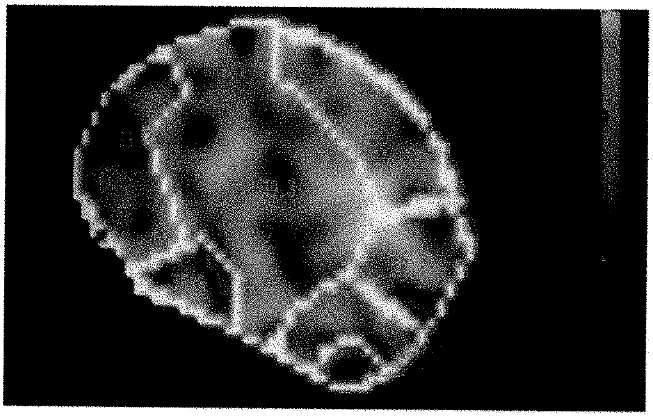

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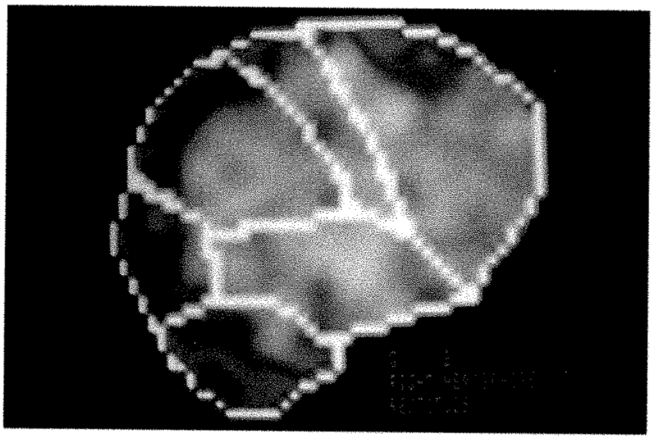

Figure 7.

flow decrease of less than 10% in three cases (Table 2). In two of these cases, the decrease took place on the opposite side to the rotation side; in the third case, it appeared bilaterally and simultaneously in the vertebrobasilar and cerebral hemispheric circulations. In a fourth case (case 1), the blood flow decrease appeared solely in the hemispheric cerebral territory.

The acetazolamide test showed poor reactivity (increase in rCBF <15%) in the brain stem–cerebellar region in four of six cases (Table 2). When the hemispheric blood flow reactivity was studied, two cases (cases 1 and 4) could be considered specific acetazolamide vertebrobasilar nonresponders. Case 1 showed a unilateral nucleus of vertebrobasilar acetazolamide-resistant oligemia on the right side (Fig 7).

NHVBI With Cerebral Insufficiency (n = 9).—In this group, NHVBI was associated with an overall decrease of hemispheric rCBF lower than 35 ± 2.8 mL/100 g per minute (Table 1). The cerebral insufficiency was either scattered in identifiable oligemic zones (five cases) or fairly global (four cases). Of four patients tested (Table 3), acetazolamide studies showed a poor reactivity (increase in rCBF <15%) in two cases. Patient 10 showed bilateral vertebrobasilar acetazolamide resistance. Rotation studies showed a global and bilateral decrease in blood flow in two cases, indicating again that the rotation test was neither vertebrobasilar specific nor side specific.

Table 2.—Influence of Head Rotation and Acetazolamide on Brain Stem–Cerebellum Regional Cerebral Blood Flow (rCBF) Values in Pure Nuclear Hemodynamic Vertebrobasilar Insufficiency (NHVBI)

			Rotation Test				Acetazolamide			
	Rectitude Values		Values		Variation, %		Values		Variation, %	
Patients	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
1	28.7	25.6	30.8	26.9	+7	+5	46.4*	44.3	+62	+73
2	32.3	35.1	35.9	40.6	+11	+16	32.7	39.2	+1	+12
3	40.6	36.7	35.6	37.3	−12	+2	34.2	39.3	−16	+7
4	38.1	30.8	31.6	31.7	−17	+3	43.3	40.6	+14	+32
5	35.5	39.1	38.5	44.9	+8	+15	44.8	45.9	+26	+17
6	42.9	36.1	32.8	26.8	−24	−26	44.5	44.7	+4	+24

*Despite the global reactivity of the brain stem–cerebellar region, a zone of inferior vertebrobasilar nonreactivity was observed (Fig 4).

Table 3.—Influence of Head Rotation and Acetazolamide on Brain Stem–Cerebellum Regional Cerebral Blood Flow Values in Nuclear Hemodynamic Vertebrobasilar Insufficiency with Cerebral Insufficiency

			Rotation Test				Acetazolamide Test			
	Rectitude Values		Values		Variation, %		Values		Variation, %	
Patients	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**	**R**	**L**
8	35.1	37.2	42.0	39.7	+20	+7	57.9	60.2	+65	+62
10	34.6	36.2	30.1	27.9	−13	−23	39.2	36.0	+13	−1
12	30.6	29.0	25.3	24.6	−17	−15	27.3	27.4	−11	−6
15	25.6	22.3	29.1	28.3	+14	+27	52.3	46.7	+104	+109

Nucleoangiographic Correlations

Table 4 presents the angiographic findings with causative data. It shows that NHVBI is strongly associated with angiographic abnormalities of the vertebrobasilar system (classification 1): 14 of 15 patients exhibited angiographically visible partial or complete arterial occlusion of the vertebrobasilar system. The abnormalities were solely extracranial in five cases, solely intracranial in three cases (Figs 8 and 9), and were both intracranial and extracranial in six cases (Fig 10). The synthesis of the 14 vertebrobasilar lesions (classification 2) is given in Table 5: the remaining patient (patient 6) had a right-sided carotid occlusion with a right posterior communicating artery steal syndrome, drawing blood from the vertebrobasilar system to the right intracranial carotid system. This patient had pure NHVBI on the left side and no hemispheric cerebral blood flow decrease on the side of the carotid thrombosis.

Table 6 shows the correlation between the side of the presumably dominant or unilateral vertebrobasilar primary lesion and the side of the dominant brain stem–cerebellar oligemia: a concordance in 10 of 13 patients was found.

The associated lesions included unilateral or bilateral lack of posterior communicating artery of the Willis polygon in five cases. Atheroma of the carotid artery was only observed in three cases of the group with NHVBI with cerebral insufficiency.

Nucleoclinical Correlations

Three types of neurologic manifestations were observed in the group of patients with NHVBI, as described below.

Vertebrobasilar Transient Ischemic Attacks.—The manifestation of vertebrobasilar transient ischemic attacks (Table 7) was classically defined as a neurologic deficit lasting less than 24 hours, subjectively considered by the patients as a true attack. It was observed in only one case and resulted in left inferior limb paresia (case 12).

Intermittent Vertebrobasilar Symptoms.—The manifestation of intermittent vertebrobasilar symptoms was defined as symptoms each lasting less than 1 hour and occurring more than three times. They could actually be repeated several times during a day or a week, for months and years. We could not classify these symptoms as transient ischemic attacks. An analysis of these symptoms is given in Table 7. Patients with NHVBI with cerebral insufficiency had the same symptoms as patients with pure NHVBI; episodic ataxia was slightly more frequent, while drop attacks and atypical falls were equally represented.

A correlation between the side of the clinically aggressive rotation and the side of the dominant brain stem–cerebellar oligemia was studied in the two groups. No clear relationship could be observed.

Vertebrobasilar Hemodynamic Threatening Syndrome.—In one case (case 8), the intermittent symptoms became virtually uninterrupted and provoked a permanent vertigo and constant unsteadiness—vestibular and cerebellar—for more than 7 days. A CT scan and a magnetic resonance image showed no infarcts or lacunae, while a marked decrease of brain stem–cerebellar blood flow was observed with associ-

Table 4.—Causative and Angiographic Findings*

Patient Characterization						
Case/ Age, y/ Sex	Hypertension		Hyperlipemia	Tobacco Consumption	Diabetes	Angiographic Findings
	Past	Now				
1/64/F				+		Atheromatous plaque on R intracranial vertebral artery; extreme narrowing of R PICA; stenosis of L intracranial vertebral artery, narrowing of L PICA; global inferior cerebellar oligemia
2/78/F			+			Hypoplasia of L extracranial vertebral artery with abnormal origin from aortic arch
3/38/M			+	+		Extrinsic stenosis of extracranial L vertebral artery at C-2 level; lack of 2 communicating posterior arteries of the Willis polygon
4/39/M						Relative stenosis of the two extracranial vertebral arteries at origin; severe stenosis of basilar artery, stenosis of L intracranial vertebral artery; distal stop on L PICA
5/64/M				+		Discrete stenosis of R AICA; atheromatous plaque of L intracranial vertebral artery; lack of 2 communicating posterior arteries of the Willis polygon
6/79/M	+	+				Thrombosis of R extracranial internal carotid artery; basilocarotidian steal via R communicating posterior artery
7/53/F			+			Marked hypoplasia of R extracranial vertebral artery; neck muscular anastomoses with branches of R subclavian artery; lack of 2 communicating posterior arteries of Willis polygon
8/53/F	+	+	+	+		Hypoplasia of R extracranial vertebral artery; R PICA invisible; lack of 2 communicating posterior arteries of the Willis polygon
9/73/M	+	+	+	+		Plicature of L extracranial vertebral artery near the origin; stenosis of L intracranial vertebral artery; L PICA invisible; lack of 2 communicating posterior arteries; mild R carotid syphon stenosis; plaque of the L internal carotid artery at origin
10/68/F	+	+				Stenosis of prevertebral R subclavian artery; hypoplasia of R extracranial vertebral artery; ostial stenosis of L vertebral artery
11/50/F				+		Stenosis of L intracranial vertebral artery; hypoplasia of L PICA
12/68/M						Hypoplasia of R extracranial vertebral artery; narrowing of R SCA; narrowing of R PICA; lack of 2 posterior communicating arteries; atheroma of R carotidian syphon; plaque on the extracranial internal carotid artery
13/64/F						Hypoplasia of R extracranial vertebral artery
14/65/M			+			Plicature of R extracranial vertebral artery; stenosis of R intracranial vertebral artery; atheromatous plaque on R extracranial internal carotid artery
15/67/F	+	+				Flexuosity of L extracranial vertebral artery after the origin; stenosis of L PICA and narrowing of L SCA

*Plus sign indicates present; PICA, posterior-inferior cerebellar artery; AICA, anterior-inferior cerebellar artery; and SCA, superior cerebellar artery.

ated hemispheric oligemia. This syndrome was reversible with high doses of a parenteral vasodilatator (nafronyl oxalate [Naftidofluryl]) given for 2 weeks. A subsequent CT scan and a magnetic resonance image showed no infarcts or lacunae. The total reversibility of the syndrome with the vasodilatator was observed 1 month after onset.

COMMENT

Nuclear Vertebrobasilar Insufficiency Indicates a Definite Vertebrobasilar Hemodynamic Deficit

When coining the term *vertebrobasilar insufficiency,* Denny-Brown[1,2] clearly defined its hemodynamic importance by indicating that it corresponded to repeated "hemodynamic crisis," distinct from emboli. However, in another conception developed early by Millikan and Siekert,[3] the intermittent symptoms could also precede thrombotic or embolic basilar occlusions and were comparable with premonitory carotid transient ischemic attacks. The term *vertebrobasilar transient ischemic attacks,* widely accepted as corresponding to vertebrobasilar insufficiency,[5,12-17] thus implies a thromboembolic theory of this condition.

Thromboembolic cases do exist in vertebrobasilar disease. Yet, for strictly vertebrobasilar insufficiency, the hemodynamic theory has frequently been supported. Compression of the vertebral artery by cervical spondylosis was described by Sheehan et al[18] in 1960. Reversal blood flow through the vertebral artery[19] and hemodynamic steal of the vertebrobasilar system due to stenosis of the subclavian artery, with intermittent symptoms, were described by Contorni[20] and Fisher.[21] Carotid steal syndromes, due to internal carotid occlusion or tight stenosis, have been postulated[22] and angiographically proved.[23,24] Again, in 1970, Fisher[25] described five patients with occlusion of proximal vertebral arteries. He did not describe the clinical manifestations as vertebrobasilar transient ischemic attacks but as "transient basilar symptoms" or "transient episodes." He pointed out that these types of lesions rarely produce infarcts in the brain stem.

Moreover, the importance of circulation-influencing factors, such as orthostatic hypotension,[1,12,26,27] orthostatism without hypotension,[28] and rotation or extension of the head,[29-31] have been underlined in vertebrobasilar insufficiency.

Finally, all the successful vascular surgery in vertebrobasilar insufficiency was mainly based on the hemodynamic theory. Extracranial vertebral artery surgery has been performed since 1957.[32-36] Intracranial revascularization was first proposed by Ausman et al.[37] Extracranial-to-intracranial bypass from the occipital artery to the posterior-inferior cerebellar artery was performed.[38-40] Anastosomis of the occipital artery to the anterior-inferior cerebellar artery[41] or of the temporal artery to the superior cerebellar artery[42-44] were also proposed. Hopkins et al[45] presented their experience of revascularization and intracranial endarterectomy in 45 patients: a relief of symptoms took place in 91% of the patients, suggesting that they were of hemodynamic origin. However, in these clinical, surgical, and ra-

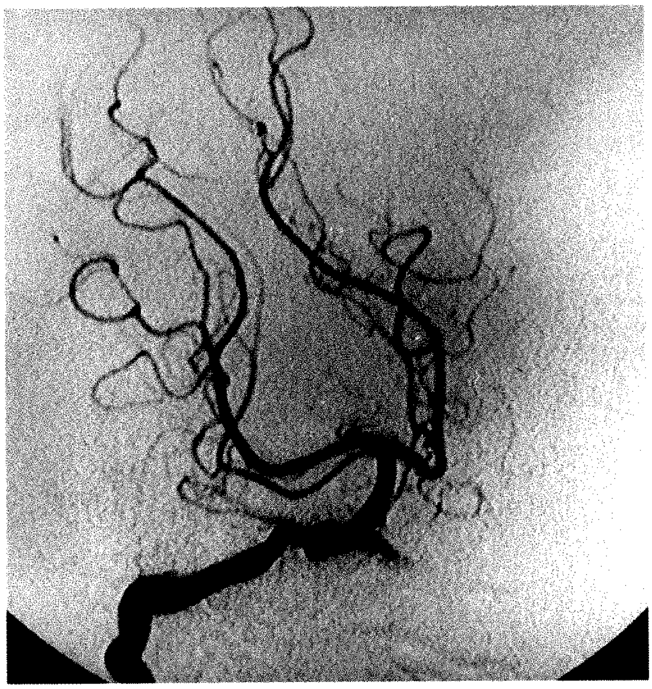

Fig 8.—Case 1. Angiographic findings included right-sided intracranial vertebral stenosis and extreme narrowing of the right posterior-inferior cerebellar artery.

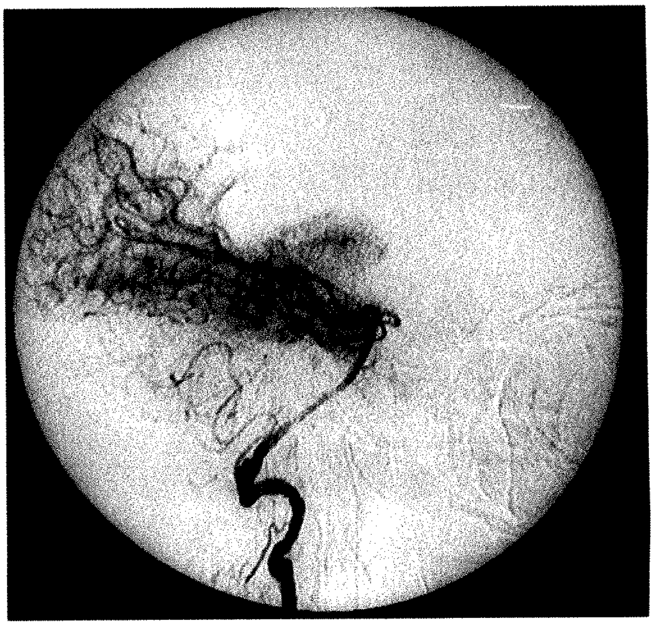

Fig 9.—Case 1. Angiographic findings (profile) included left-sided intracranial vertebral stenosis, narrowing of the left posterior-inferior cerebellar artery with radiologic oligemia of the cerebellum. Note the absence of collateral vessels between the posterior-inferior cerebellar artery and superior cerebellar artery territories.

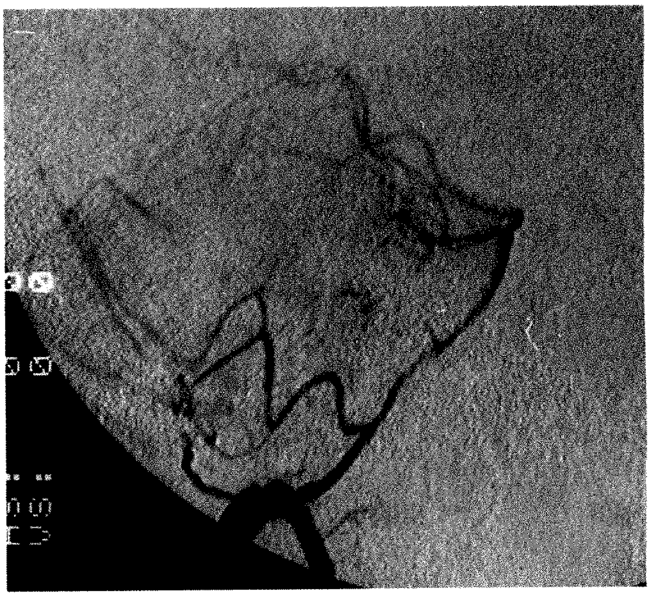

Fig 10.—Case 4. Angiographic findings on the side of nuclear vertebrobasilar insufficiency (left). Note the stenosis of the intracranial vertebral artery and the basilar artery. A distal stop of the left posterior-inferior cerebellar artery was observed. Tiny collateral vessels seemed to exist. This patient also had a partial stenosis of the two extracranial vertebral arteries at origin.

diologic approaches, the blood flow measurements were not available to give definite support to the hemodynamic theory.

Blood flow measurement does allow a hemodynamic diagnosis. The normal value of blood flow in the brain stem was determined by Brown and Donaldson,[46] with direct injection of ^{133}Xe in the vertebral artery, to be 59 mL/100 g per minute. Shirahata et al[47] mentioned a value of 54 ± 6 mL/100 g per minute with the ^{133}Xe inhalation technique. In our laboratory, the mean value in controls is 54.3 ± 4.3 mL/100 g per minute on the right side and 52.0 ± 5.5 on the left side. Naritomi et al[7] studied patients with clinical vertebrobasilar insufficiency who exhibited transient ischemic attacks and measured the cerebral blood flow after 1 minute with the ^{133}Xe inhalation technique. With the subject in the supine position, the mean brain stem cerebellar value was 97.1 ± 15.7 mL/100 g per minute, which is high. No substantial decrease of the mean brain stem–cerebellar value was observed in patients when compared with the mean value of controls. According to Naritomi et al,[7] this group of patients was characterized by a marked brain stem–cerebellar and hemispheric blood flow decrease, after orthostatic postural tilt-

Table 5.—Summary of Primary Vertebrobasilar Angiographically Detected Lesions in 14 Patients With Nuclear Hemodynamic Vertebrobasilar Insufficiency

Variables	R	L
Extracranial		
Hypoplasia of extracranial vertebral artery	5	1
Extrinsic stenosis	. . .	1
Stenosis at origin	1	2
Kinking or flexuosity near the origin	2	2
Intracranial*		
Stenosis or narrowing of distal vertebral artery	2	5
Stenosis or hypoplasia of basilar artery	. . . 1 . . .	
Occlusion, stenosis, or narrowing of		
PICA	3	5
AICA	1	. . .
SCA	1	1

*PICA indicates posterior-inferior cerebellar artery; AICA, anterior-inferior cerebellar artery; and SCA, superior cerebellar artery.

Table 6.—Correlation Between the Side of the Dominant Angiographic Vertebrobasilar Lesions and the Side of the Dominant Nuclear Brain Stem Cerebellum Oligemia*

Patients	Side of the Dominant Angiographic Lesion	Sideof theDominant NuclearOligemia	Concordance
Pure NHVBI			
1	R	L	No
2	L	R	No
3	L	L	Yes
4	L	L	Yes
5	L	R	Yes
6	. . .	. . .	. . .
NHVBI with cerebral insufficiency			
7	R	R	Yes
8	R	R	Yes
9	L	L	Yes
10	. . .	. . .	. . .
11	L	L	Yes
12	R	L	No
13	R	R	Yes
14	R	R	Yes
15	L	L	Yes

*NHVBI indicates nuclear hemodynamic vertebrobasilar insufficiency.

Table 7.—TIAs, Intermittent Symptoms, and Vertebrobasilar Threatening Syndrome in NHVBI*

		Intermittent Symptoms										
Patient	TIAs	Time of Evolution, mo	Influence of Position	Vertigo	Ataxia	Falling	True Drop Attack	Lipothymia	Diplopia	Visual Signs	Headache	Vertebrobasilar Threatening Syndrome
1		18	E	+		+						
2		72	O		+				+		+	
3		1	ERO	+	+	+						
4		24					+				+	
5		2	EO	+				+		+		
6		4		+	+							
7		72	RO	+								
8		48	O	+	+							+
9		1		+	+		+					
10		6	RO	+		+			+	+	+	
11		4		+	+						+	
12	+	24	R	+	+							
13		36	O		+	+						
14		24			+	+						
15		12	RO		+					+		

*TIAs indicates transient ischemic attacks; NHVBI, nuclear hemodynamic vertebrobasilar insufficiency; E, extension of head; R, rotation of head; O, orthostatism; and plus sign, present.

ing by 30°, suggesting a generalized dysautoregulation. With use of the HM-PAO–^{99m}Tc technique, Sakai et al[48] studied a patient with spondylotic stenosis of the vertebral artery that had been angiographically confirmed. There was no decrease of the cerebellar blood flow, either in the supine position or in the orthostatic position. The rotation of the head to the left in the orthostatic position provoked a decrease of blood flow in the right occipital region and in the left cerebellar hemisphere.

In 1989, we[49] mentioned in a preliminary abstract that severe NHVBI could be diagnosed in several patients in the supine position, when ^{133}Xe inhalation blood flow measurements were performed. Preliminary angiographic and clinical findings were presented. The preliminary findings of several acetazolamide tests were also given, showing that a vertebrobasilar reactivity lacked in about half of the cases. Delecluse et al,[50] using ^{133}Xe inhalation single-photon emission CT described a patient with decreased right-sided cerebellar perfusion that did not react to acetazolamide.

In this study, we can confirm that there is a considerable group of patients with permanent NHVBI, observed with the classic blood flow measurement in the supine position. The values observed are far below the range for normal controls and even for patients with asymptomatic carotid stenosis.

The proposed threshold of 35 mL/100 g per minute was not experimentally founded. Ischemic penumbra was shown to occur at 23 mL/100 g per minute.[51] However, a growing consensus of investigators tend to consider 35 mL/100 g per minute a putative threshold of oligemia.[9] Yet, this limit of 35 mL/100 g per minute seems to be clinically valuable, because all the patients selected on this basis exhibited intermittent manifestations corresponding well to the vertebrobasilar hemodynamic crises originally described by Denny-Brown.[1,2] In these patients, the hemodynamic theory of vertebrobasilar insufficiency is thus demonstrated.

It is possible that milder levels of ischemia, greater than 35±2.8 mL/100 g per minute, might belong to the syndrome of NHVBI. Studies with a clinical basis of selection are needed to investigate this point.

This hemodynamic restriction has been documented in 10 cases by rotation and acetazolamide studies. Rotation tests showed rare specifically vertebrobasilar contralateral effects (in two of 10 patients) and global blood flow decrease (in three of 10 patients). These hemodynamic data do not confirm the classic contralateral specific vertebrobasilar effects of the rotation test but do confirm in vivo the random vertebral flow decrease induced by head rotation observed in cadavers by Toole and Tucker.[29]

Acetazolamide tests showed a poor vasodilatory capacity in the posterior circulation in more than half the patients. Some patients appeared to be specific vertebrobasilar acetazolamide nonresponders. In case 1, in which the posterior-inferior cerebellar artery was occluded, acetazolamide resistance was observed in the corresponding region.

Vascular Importance of Nucleovertebrobasilar Insufficiency

Primary arterial vertebrobasilar abnormalities have been diagnosed by angiography in 14 of 15 cases. A basilar carotid steal syndrome was also found in the 15th case. Thus, blood flow measurement of the brain stem–cerebellar region appears to be a very good indicator of the vertebrobasilar arterial circulation.

When compared with the classic angiographic series of Meyer et al[5] and Caplan and Rosenbaum,[6] our series shows a greater proportion of possibly malformative extracranial abnormalities, particularly extracranial vertebral hypoplasia, and a lower proportion of intracranial vertebral and basilar stenosis or occlusions.

The intracranial lesions in our series included unilateral or bilateral intracranial vertebral artery stenosis, as already described. The finding of vertebrobasilar insufficiency with bilateral stenosis of intracranial vertebral arteries has been reported by Ausman et al,[37,41] Roski et al,[39] Hopkins et al,[52] and Sundt et al.[53,54] Caplan[55] has recently highlighted the prominent hemodynamic permanent deficit provoked by bilateral occlusions of the intracranial vertebral artery stenosis, due to the absence of collateral vessels. In patient 1, who had such a syndrome, this hemodynamic deficit was clearly confirmed. However, our data also show that, with unilateral intracranial vertebral stenosis only, a hemodynamic deficit can occur. Absence of collateral vessels was also found in our cases, inducing a radiologic oligemia of the cerebellum.

Abnormalities of basilar branches—stenosis, narrowing, or occlusion—were also detected in our series, particularly at the level of the posterior-inferior cerebellar artery. Besides acute "basilar branch disease," as described by Fisher and Caplan[56] and Caplan,[57] we suggest that these cases, in which vertebrobasilar oligemia and clinical symptoms were demonstrated, might correspond to chronic basilar branch disease.

In several cases, distal abnormalities of the vertebrobasilar intracranial system were observed. Caplan[57] indicated that vertebrobasilar insufficiency could exist without a detectable arterial lesion and might yet have a hemodynamic origin. The effect of tobacco on distal encephalic arteries has been recently proposed by Donnan et al.[58] A general observation in the patients with intracranial vertebrobasilar and distal lesions in this series is that they were heavy smokers. One could postulate that, in these cases, the arterial stenosis or occlusions were located at the level of perforating arteries and that they were aggravated by tobacco consumption.

Nucleoclinical Correlations

Vertebrobasilar oligemia (<35 mL/100 g per minute) appears to be strongly associated with intermittent basilar symptoms (15 of 15 cases). Typical vertebrobasilar transient ischemic attacks conversely were rare (one of 15 cases). Thus, the threshold of 35 mL/100 g per minute seems to also define vertebrobasilar nonthromboembolic cases. In the colorful terms of Caplan,[55] NHVBI is related to "smoke" but not to "fire" (infarct).

The physiopathologic features of these intermittent vertebrobasilar symptoms should be discussed. Complete remission and repetition of the phenomenon suggests a purely neurophysiologic origin, consisting of short interruptions of synaptic transmission and neuronal function.

Below the limit of 35 mL/100 g per minute, a borderline hemodynamic state would exist, with an unstable metabolic compensation. The discovery of the physiologic increase of cerebellar blood flow with voluntary movements[59] might account for some of these symptoms. Insufficient posterior circulation would be unable to supply the functional increase in blood flow, so that a hemodynamic crisis due to neurophysiologic activation might then occur. Aggravation of the symptoms by orthostatism would then have an explanation other than simple orthostatic hypotension; it might also be due to the "switching on" of static cerebellar function, with a hemodynamic crisis at the level of the cerebellum and related structures.

Finally, this syndrome would be comparable with the "misery perfusion syndrome" at the hemispheric level, which includes intermittent symptoms and a compensation of oligemia by an increase of the extraction fraction of oxygen.[60]

Vertebrobasilar threatening syndrome, which was represented by one patient in our series, might correspond to the failure of the metabolic compensation of vertebrobasilar oligemia. In this field, vertebrobasilar bypass surgery finds its best theorical justification. Revascularization experiments demonstrated, in some cases, the disappearance of intermittent symptoms with improvement of the blood supply.[37,39,41,45,52-54]

In conclusion, we believe that blood flow measurement by the ^{133}Xe technique is a valuable method by which to diagnose a true hemodynamic deficit of the vertebrobasilar circulation. Imaging of a NHVBI is an easy, reproducible, and unaggressive way to confirm the clinical diagnosis of vertebrobasilar insufficiency. It might provide objective data to evaluate the effect of revascularization surgery.

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References

1. Denny-Brown D. The treatment of recurrent cerebrovascular symptoms and the question of 'vasospasm.' *Med Clin North Am.* 1951;35:1457-1474.
2. Denny-Brown D. Basilar artery syndromes. *Bull N Engl Med Center.* 1953;15:53-60.
3. Millikan OH, Siekert RG. Studies in cerebrovascular disease, 1: the syndrome of intermittent insufficiency of the basilar arterial system. *Proc Staff Meet Mayo Clin.* 1955;30:61-68.
4. Hangsted H. Occlusion of the basilar artery: diagnosis by vertebral angiography during life. *Neurology.* 1956;6:823-828.
5. Meyer JS, Sheehan S, Bauer B. An arteriographic study of cerebrovascular disease in man. *Arch Neurol.* 1960;2:27-45.

6. Caplan LR, Rosenbaum AE. Role of cerebral angiography in vertebrobasilar occlusive disease. *J Neurol Neurosurg Psychiatry*. 1975;38:601-612.

7. Naritomi H, Sakai F, Meyer JS. Pathogenesis of transient ischemic attacks within the vertebrobasilar arterial system. *Arch Neurol*. 1979;36:121-128.

8. Fox RA, Knuckey RF, Fleay RF, Stokes B, Van Der Schaaf A, Surveyor I. Regional cerebral blood flow utilizing the gamma-camera and xenon inhalation: reproducibility and clinical applications. *Stroke*. 1985;16:1010-1015.

9. Baron JC Phénomènes physiopathologiques au cours de l'ischémie focale aiguë du cerveau. *Rev Med*. 1983;38:1853-1863.

10. Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal ischemia in awake monkey. *J Neurosurg*. 1982;54:773-782.

11. Vorstrup S, Brun B, Lassen NA. Evaluation of the cerebral vasodilatory capacity by the acetazolamide test before EC-IC bypass surgery in patients with occlusion of the internal carotid artery. *Stroke*. 1986;17:1291-1298.

12. Williams D, Wilson TG. The diagnosis of the major and minor syndromes of basilar insufficiency. *Brain*. 1962;85:741-774.

13. Marshall J. The natural history of transient ischemic cerebro-vascular arteries. *Q J Med*. 1964;33:309-324.

14. Whisnant JP, Cartlidge NEF, Elvebach LR. Carotid and vertebral basilar ischemic attacks: effects of anticoagulants, hypertension and cardiac disorders in survival and stroke occurrence: a population study. *Ann Neurol*. 1978;3:107-115.

15. Ueda K, Toole JF, McHenry LC. Carotid and vertebrobasilar transient ischemic attacks: clinical and angiographic correlations. *Neurology*. 1979;29:1004-1101.

16. Millikan CH, Siekert RG, Sekhick RM. Studies in cerebrovascular disease, II: the use of anticoagulant drugs in the treatment of insufficiency or thrombosis within the basilar arterial system. *Proc Staff Meet Mayo Clin*. 1955;30:116-126.

17. Wright IS, Mc Devitte E. Cerebral vascular diseases: their significant diagnosis and treatment, including the use of anticoagulant substances. *Ann Intern Med*. 1954;41:682-688.

18. Sheehan S, Bauer R, Meyer JS. Vertebral artery compression in cervical spondylosis. *Neurology*. 1960;10:968-986.

19. Reivich H, Holling HE, Robert B, Toole JF. Reversal of blood flow through the vertebral artery and its effect on cerebral circulation. *N Engl J Med*. 1961;265:878-885.

20. Contorni L. El circolo collaterale vertebro-vertebrale nella obliterazione dell'arteria suc clavia alla sue origine. *Minerva Chir*. 1960;15:268-271.

21. Fisher CM. A new vascular syndrome: 'the subclavian steal.' *N Engl J Med*. 1961;265:912-913.

22. Humphries AW, Young JR, Beven EG, et al. Relief of vertebrobasilar symptoms by carotid endarterectomy. *Surgery*. 1965;57:48-52.

23. Schott B, Michel D, Goutelle A. Sténoses et thromboses carotidiennes à expression vertébrobasilaire: hémodétournement. *Rev Neurol Paris*. 1964;121:501-514.

24. Bogousslavsky J, Regli F. Vertebrobasilar transient ischemic attacks in internal carotid artery occlusion or tight stenosis. *Arch Neurol*. 1985;42:64-68.

25. Fisher CM. Occlusion of the vertebral artery causing transient basilar symptoms. *Arch Neurol*. 1970;22:13-19.

26. Williams D. Vertebrobasilar ischemia. *BJM*. 1964;1:84-86.

27. Loeb C, Meyer JS, eds. *Strokes Due to Vertebrobasilar Disease*. Springfield, Ill: Charles C Thomas Publisher; 1965:136-173.

28. Caplan LR, Sergay S. Positional cerebral ischaemia. *J Neurol Neurosurg Psychiatry*. 1976;39:385-391.

29. Toole JF, Tucker SH. Influence of head position upon cerebral circulation. *Arch Neurol*. 1960;2:616-623.

30. Mehalic T, Farhat S. Vertebral artery injury form chiropractic manipulation of the neck. *Bull Johns Hopkins Hosp*. 1956;98:37-42.

31. Hardin C. Vertebral artery insufficiency produced by cervical osteoarthrotic spurs. *Arch Surg*. 1965;90:629-633.

32. Crawford ES, De Bakey ME, Fields WS. Roentgenographic diagnosis and surgical treatment of basilar artery insufficiency. *JAMA*. 1958;168:509-514.

33. Cate WR, Scott HN Jr. Cerebral ischemia of central origin relieved by subclavian–vertebral artery thromboendarterectomy. *Surgery*. 1959;45:19-31.

34. De Bakey ME, Crawford ES, Morris GC, et al. Surgical consideration of occlusive disease of the innominate carotid, subclavian and vertebral arteries. *Ann Surg*. 1961;154:698-725.

35. Labauge R, Thevenet A, Crouzet G, Nicolas M. Les insuffisances vertébrobasilaires d'incidence chirurgicale (à propos de 87 malades opérés). *Rev Neurol*. 1967;117:373-389.

36. Baker R, Rossenbaum A, Caplan L. Subclavian steal syndrome. *Contemp Surg*. 1974;4:96-104.

37. Ausman J, Nicoloff D, Chou S. Posterior revascularization: anastomosis of vertebral artery to PICA with interposed radial artery. *Surg Neurol*. 1978;9:281-286.

38. Sundt TM Jr, Piepgras DG. Occipital posterior inferior cerebellar artery bypass surgery. *J Neurosurg*. 1978;48:916-928.

39. Roski RA, Spetzler RF, Hopkins L. Occipital artery to posterior inferior cerebellar artery by pass for vertebrobasilar ischemia. *Neurosurgery*. 1982;10:44-49.

40. Khodadad C. Occipital artery–posterior inferior cerebellar artery anastomosis. *Surg Neurol*. ; 1976;5:225-227.

41. Ausman JL, Diaz FG, de los Ryes RA, Boulos R. Anastomosis of occipital artery to anterior inferior cerebellar artery for vertebrobasilar junction stenosis. *Surg Neurol*. 1981;16:99-102.

42. Ausman J, Lee MC, Chater N, Pak H, Patel S, Boulos R. Superficial temporal artery to superior cerebellar artery anastomosis for distal basilar artery stenosis. *Surg Neurol*. 1979;12:277-282.

43. Ausman JC, Diaz FG, de los Reyes RA, et al. Superficial temporal to proximal superior cerebellar artery anastomosis for basilar artery stenosis. *Neurosurgery*. 1981;9:56-60.

44. Ausman JC, Diaz FG, de los Reyes RA, et al. Superficial temporal to superior cerebellar artery anastomosis. *J Neurosurg*. 1982;56:766-776.

45. Hopkins LN, Martin NA, Hadley MN, Spetzler RF, Budny J, Caster LP. Vertebrobasilar insufficiency, II: microsurgical treatment of intracranial vertebrobasilar disease. *J Neurosurg*. 1987;66:662-674.

46. Brown AS, Donaldson AA. Clinical vertebral artery cerebral blood flow measurement. *Eur Neurol*. 1971-72;6:274-276.

47. Shirahata N, Henriksen L, Vorstrup S, et al. Regional cerebral blood flow assessed by 133 Xe inhalation and emission tomography: normal values. *J Comput Assist Tomogr*. 1985;9:861-866.

48. Sakai F, Ishi K, Garashi H, et al. Regional cerebral blood flow during an attack of vertebrobasilar insufficiency. *Stroke*. 1988;19:1426-1430.

49. Trouillas P, Philippon B, Nighoghossian N. Insuffisance vertébrobasilaire hemodynamique démontrée par les débits cérébraux et ataxie cerebelleuse chronique oligemique: deux nouveaux concepts. *C R Acad Sci III*. 1989;309:755-762.

50. Delecluse F, Voordecker P, Raftopoulos Ch. Vertebrobasilar insufficiency revealed by 133 Xenon inhalation SPECT. *Stroke*. 1989;20:952-956.

51. Astrup J, Siesjo Bok, Symon L. Threshold in cerebral ischemia: the ischemic penumbra. *Stroke*. 1981;12:723-725.

52. Hopkins L, Budney J, Stetzler R. Revascularization of the vertebral brain stem. *Neurosurgery*. 1982;10:364-369.

53. Sundt T, Piepgras D, Campbell J, Holman C. Intracranial by pass grafts for vertebrobasilar ischemia. *Mayo Clin Proc*. 1978;53:12-18.

54. Sundt T, Piepgras D, Houser O, Campbell J. Interposition saphenous vein grafts for advanced occlusive disease and large aneurysms in the posterior circulation. *J Neurosurg*. 1982;56:205-215.

55. Caplan LR. Bilateral distal vertebral artery occlusion. *Neurology*. 1983;33:552-558.

56. Fisher CM, Caplan LR. Basilar artery branch occlusion: a cause of pontine infarction. *Neurology*. 1971;21:900-905.

57. Caplan LR. Vertebrobasilar disease: time for a new strategy. *Stroke*. 1981;12:111-114.

58. Donnan G, Adena MA, O'Malley H, Mc Neil JJ, Doyle AE, Neil GC. Smoking is a risk factor for cerebral ischemia. *Lancet*. 1989;2:643-647.

59. Decety J, Philippon B, Ingvar DH. rCBF landscapes during motor performances and motor ideation of a graphic gesture. *Eur Arch Psychiatry Neurol Sci*. 1988;238:33-38.

60. Baron JC, Bousser MG, Rey A, Guillard A, Comar D, Castaigne P. Reversal of focal 'misery-perfusion syndrome' by extra-intracranial arterial bypass in hemodynamic cerebral ischemia: a case study with ^{15}O positron emission tomography. *Stroke*. 1981;12:454-459.

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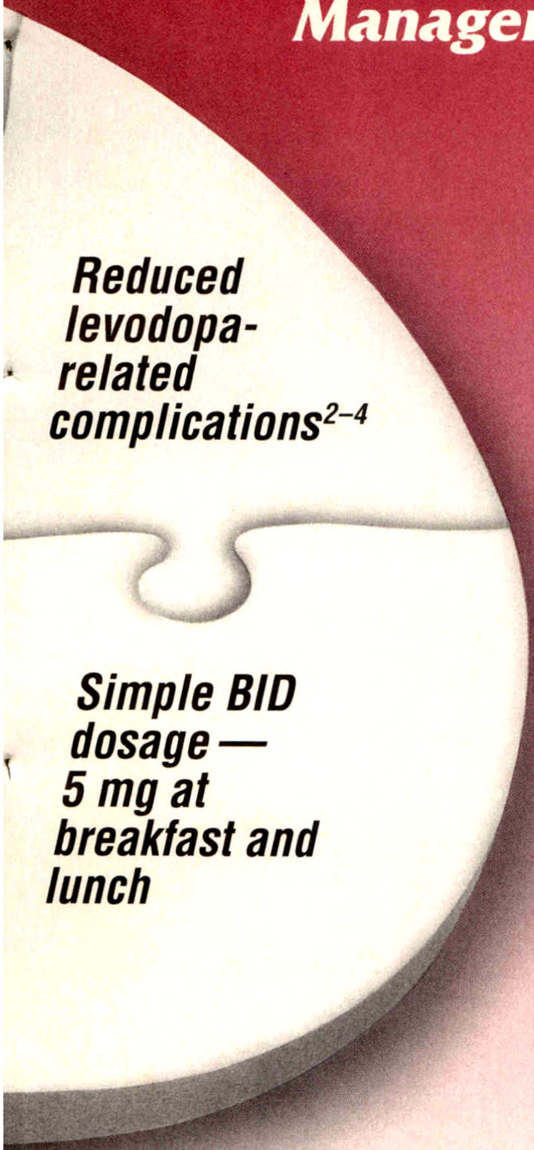
still a puzzle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(SELEGILINE HYDROCHLORIDE)

Fits your therapeutic strategy

*Higher doses have not been shown to increase benefit and have increased the risk of side effects. Please see Dosage and Administration section of prescribing information.

†Further reduction of levodopa/carbidopa may be possible during continued selegiline therapy.

See next page for brief summary of prescribing information.

Eldepryl®

(SELEGILINE HYDROCHLORIDE)

BRIEF SUMMARY

CLINICAL PHARMACOLOGY:

The mechanisms accounting for selegiline's beneficial adjunctive action in the treatment of Parkinson's disease are not fully understood. Inhibition of monoamine oxidase, type B, activity is generally considered to be of primary importance; in addition, there is evidence that selegiline may act through other mechanisms to increase dopaminergic activity.

INDICATIONS AND USAGE:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is indicated as an adjunct in the management of Parkinsonian patients being treated with levodopa/carbidopa who exhibit deterioration in the quality of their response to this therapy. There is no evidence from controlled studies that selegiline has any beneficial effect in the absence of concurrent levodopa therapy.

Evidence supporting this claim was obtained in randomized controlled clinical investigations that compared the effects of added selegiline or placebo in patients receiving levodopa/carbidopa. Selegiline was significantly superior to placebo on all three principal outcome measures employed: change from baseline in daily levodopa/carbidopa dose, the amount of 'off' time, and patient self-rating of treatment success. Beneficial effects were also observed on other measures of treatment success (e.g., measures of reduced end of dose akinesia, decreased tremor and sialorrhea, improved speech and dressing ability and improved overall disability as assessed by walking and comparison to previous state).

CONTRAINDICATIONS:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is contraindicated in patients with a known hypersensitivity to this drug.

WARNINGS:

Selegiline should not be used at daily doses exceeding those recommended (10 mg/day) because of the risks associated with non-selective inhibition of MAO. (See CLINICAL PHARMACOLOGY.)

The selectivity of selegiline for MAO B may not be absolute even at the recommended daily dose of 10 mg a day and selectivity is further diminished with increasing daily doses. The precise dose at which selegiline becomes a non-selective inhibitor of all MAO is unknown, but may be in the range of 30 to 40 mg a day.

Because of reports of fatal interactions, MAOIs are ordinarily contraindicated for use with meperidine (DEMEROL & other tradenames). This warning is often extended to other opioids. Because the mechanism of interaction between MAOIs and meperidine is unknown, it seems prudent, in general, to avoid this combination.

Definitive clinical data on the concomitant use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) and fluoxetine hydrochloride (PROZAC) is not available. Death has been reported to occur following the initiation of therapy with nonselective MAOI's (NARDIL, PARNATE) shortly after discontinuation of fluoxetine. To date, this reaction has not been reported with ELDEPRYL® (SELEGILINE HYDROCHLORIDE), however, since the mechanism of this reaction is not fully understood it seems prudent, in general, to avoid this combination. Because of the long half-lives of fluoxetine and its active metabolite, at least five weeks (approximately 5 half-lives) should elapse beweeen discontinuation of fluoxetine and initiation of MAOI therapy. Based on experience with the combined use of MAOI's and tricyclic antidepressants, at least 14 days should elapse between discontinuation of an MAOI and initiation of treatment with fluoxetine.

PRECAUTIONS:

General: Some patients given selegiline may experience an exacerbation of levodopa associated side effects, presumably due to the increased amounts of dopamine reacting with super-sensitive post-synaptic receptors. These effects may often be mitigated by reducing the dose of levodopa/carbidopa by approximately 10 to 30%.

The decision to prescribe selegiline should take into consideration that the MAO system of enzymes is complex and incompletely understood and there is only a limited amount of carefully documented clinical experience with selegiline. Consequently, the full spectrum of possible responses to selegiline may not have been observed in pre-marketing evaluation of the drug. It is advisable, therefore, to observe patients closely for atypical responses.

Information for Patients: Patients should be advised of the possible need to reduce levodopa dosage after the initiation of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) therapy.

Patients (or their families if the patient is incompetent) should be advised not to exceed the daily recommended dose of 10 mg. The risk of using higher daily doses of selegiline should be explained, and a brief description of the 'cheese reaction' provided. While hypertensive reactions with selegiline have not been reported, documented experience is limited. Consequently, it may be useful to inform patients (or their families) about the signs and symptoms associated with MAOI induced hypertensive reactions. In particular, patients should be urged to report, immediately, any severe headache or other atypical or unusual symptoms not previously experienced.

Laboratory Tests: No specific laboratory tests are deemed essential for the management of patients on ELDEPRYL® (SELEGILINE HYDROCHLORIDE). Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions: No interactions attributed to the combined use of selegiline and other drugs have been reported. However, because the database of documented clinical experience is limited, the level of reassurance provided by this lack of adverse reporting is uncertain. (See WARNINGS and PRECAUTIONS.)

Carcinogenesis, Mutagenesis, and Impairment of Fertility: Studies have not been performed to date to evaluate the carcinogenic potential of selegiline hydrochloride.

Pregnancy: *Pregnancy Category C.* Insufficient animal reproduction studies have been done with selegiline to conclude that selegiline poses no teratogenic risk. However, one rat study carried out at doses as much as 180 fold the recommended human dose revealed no evidence of a teratogenic effect. It is not known whether selegiline can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Selegiline should be given to a pregnant woman only if clearly needed.

Nursing Mothers: It is not known whether selegiline hydrochloride is excreted in human milk. Because many drugs are excreted in human milk, consideration should be given to discontinuing the use of all but absolutely essential drug treatments in nursing women.

Pediatric Use: The effects of selegiline hydrochloride in children have not been evaluated.

ADVERSE REACTIONS:

Introduction: The number of patients who received selegiline in prospectively monitored pre-marketing studies is limited. While other sources of information about the use of selegiline are available (e.g., literature reports, foreign post-marketing reports, etc.) they do not provide the kind of information necessary to estimate the incidence of adverse events. Thus, overall incidence figures for adverse reactions associated with the use of selegiline cannot be provided. Many of the adverse reactions seen have been also reported as symptoms of dopamine excess.

Moreover, the importance and severity of various reactions reported often cannot be ascertained. One index of relative importance, however, is whether or not a reaction caused treatment discontinuation. In prospective pre-marketing studies, the following events led, in decreasing order of frequency, to discontinuation of treatment with selegiline: nausea, hallucinations, confusion, depression, loss of balance, insomnia, orthostatic hypotension, increased akinetic involuntary movements, agitation, arrhythmia, bradykinesia, chorea, delusions, hypertension, new or increased angina pectoris and syncope. Events reported only once as a cause of discontinuation are ankle edema, anxiety, burning lips/mouth, constipation, drowsiness/lethargy, dystonia, excess perspiration, increased freezing, gastrointestinal bleeding, hair loss, increased tremor, nervousness, weakness and weight loss.

Experience with ELDEPRYL® (SELEGILINE HYDROCHLORIDE) obtained in parallel, placebo controlled, randomized studies provides only a limited basis for estimates of adverse reaction rates. The following reactions that occurred with greater frequency among the 49 patients assigned to selegiline as compared to the 50 patients assigned to placebo in the only parallel, placebo controlled trial performed in patients with Parkinson's disease are shown in the following Table. None of these adverse reactions led to a discontinuation of treatment.

In all prospectively monitored clinical investigations, enrolling approximately 920 patients, the following adverse events, classified by body system, were reported.

CENTRAL NERVOUS SYSTEM:

Motor/Coordination/Extrapyramidal: increased tremor, chorea, loss of balance, restlessness, blepharospasm, increased bradykinesia, facial grimace, falling down, heavy leg, muscle twitch*, myoclonic jerks*, stiff neck, tardive dyskinesia, dystonic symptoms, dyskinesia, involuntary movements, freezing, festination, increased apraxia, muscle cramps.

Mental Status/Behavioral/Psychiatric: hallucinations, dizziness, confusion, anxiety, depression, drowsiness, behavior/mood change, dreams/nightmares, tiredness, delusions, disorientation, lightheadedness, impaired memory*, increased energy*, transient high*, hollow feeling, lethargy/malaise, apathy, overstimulation, vertigo, personality change, sleep disturbance, restlessness, weakness, transient irritability.

Pain/Altered Sensation: headache, back pain, leg pain, tinnitus, migraine, supraorbital pain, throat burning, generalized ache, chills, numbness of toes/fingers, taste disturbance.

AUTONOMIC NERVOUS SYSTEM: Dry mouth, blurred vision, sexual dysfunction.

CARDIOVASCULAR: Orthostatic hypotension, hypertension, arrhythmia, palpitations, new or increased angina pectoris, hypotension, tachycardia, peripheral edema, sinus bradycardia, syncope.

GASTROINTESTINAL: Nausea/vomiting, constipation, weight loss, anorexia, poor appetite, dysphagia, diarrhea, heartburn, rectal bleeding, bruxism*, gastrointestinal bleeding (exacerbation of preexisting ulcer disease).

GENITOURINARY/GYNECOLOGIC/ENDOCRINE: Slow urination, transient anorgasmia*, nocturia, prostatic hypertrophy, urinary hesitancy, urinary retention, decreased penile sensation*, urinary frequency.

SKIN AND APPENDAGES: Increased sweating, diaphoresis, facial hair, hair loss, hematoma, rash, photosensitivity.

MISCELLANEOUS: Asthma, diplopia, shortness of breath, speech affected.

POSTMARKETING REPORTS: The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ELDEPRYL® (SELEGILINE HYDROCHLORIDE).

CNS: Seizure in dialyzed chronic renal failure patient on concomitant medications.

*indicates events reported only at doses greater than 10 mg/day.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Adverse Event	Number of Patients Reporting Events	
	selegiline hydrochloride N = 49	placebo N = 50
Nausea	10	3
Dizziness/Lightheaded/Fainting	7	1
Abdominal Pain	4	2
Confusion	3	0
Hallucinations	3	1
Dry mouth	3	1
Vivid Dreams	2	0
Dyskinesias	2	5
Headache	2	1
The following events were reported once in either or both groups:		
Ache, generalized	1	0
Anxiety/Tension	1	1
Anemia	0	1
Diarrhea	1	0
Hair Loss	0	1
Insomnia	1	1
Lethargy	1	0
Leg pain	1	0
Low back pain	1	0
Malaise	0	1
Palpitations	1	0
Urinary Retention	1	0
Weight Loss	1	0

OVERDOSAGE:

Selegiline: No specific information is available about clinically significant overdoses with ELDEPRYL® (SELEGILINE HYDROCHLORIDE). However, experience gained during selegiline's development reveals that some individuals exposed to doses of 600 mg d,l selegiline suffered severe hypotension and psychomotor agitation.

Since the selective inhibition of MAO B by selegiline hydrochloride is achieved only at doses in the range recommended for the treatment of Parkinson's disease (e.g., 10 mg/day), overdoses are likely to cause significant inhibition of both MAO A and MAO B. Consequently, the signs and symptoms of overdose may resemble those observed with marketed non-selective MAO inhibitors [e.g., tranylcypromine (PARNATE), isocarboxazide (MARPLAN), and phenelzine (NARDIL)].

Overdose with Non-Selective MAO Inhibition: NOTE: This section is provided for reference; it does not describe events that have actually been observed with selegiline in overdose.

Characteristically, signs and symptoms of non-selective MAOI overdose may not appear immediately. Delays of up to 12 hours between ingestion of drug and the appearance of signs may occur. Importantly, the peak intensity of the syndrome may not be reached for upwards of a day following the overdose. Death has been reported following overdosage. Therefore, immediate hospitalization, with continuous patient observation and monitoring for a period of at least two days following the ingestion of such drugs in overdose is strongly recommended.

The clinical picture of MAOI overdose varies considerably; its severity may be a function of the amount of drug consumed. The central nervous and cardiovascular systems are prominently involved.

Signs and symptoms of overdosage may include, alone or in combination, any of the following: drowsiness, dizziness, faintness, irritability, hyperactivity, agitation, severe headache, hallucinations, trismus, opisthotonus, convulsions, and coma; rapid and irregular pulse, hypertension, hypotension and vascular collapse; precordial pain, respiratory depression and failure, hyperpyrexia, diaphoresis, and cool, clammy skin.

Treatment Suggestions for Overdose

NOTE: Because there is no recorded experience with selegiline overdose, the following suggestions are offered based upon the assumption that selegiline overdose may be modeled by non-selective MAOI poisoning. In any case, up-to-date information about the treatment of overdose can often be obtained from a certified Regional Poison Control Center. Telephone numbers of certified Poison Control Centers are listed in the Physician's Desk Reference (PDR).

Treatment of overdose with non-selective MAOIs is symptomatic and supportive. Induction of emesis or gastric lavage with instillation of charcoal slurry may be helpful in early poisoning, provided the airway has been protected against aspiration. Signs and symptoms of central nervous system stimulation, including convulsions, should be treated with diazepam, given slowly intravenously. Phenothiazine derivatives and central nervous system stimulants should be avoided. Hypotension and vascular collapse should be treated with intravenous fluids and, if necessary, blood pressure titration with an intravenous infusion of a dilute pressor agent. It should be noted that adrenergic agents may produce a markedly increased pressor response.

Respiration should be supported by appropriate measures, including management of the airway, use of supplemental oxygen, and mechanical ventilatory assistance, as required.

Body temperature should be monitored closely. Intensive management of hyperpyrexia may be required. Maintenance of fluid and electrolyte balance is essential.

DOSAGE AND ADMINISTRATION:

ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is intended for administration to Parkinsonian patients receiving levodopa/carbidopa therapy who demonstrate a deteriorating response to this treatment. The recommended regimen for the administration of ELDEPRYL® (SELEGILINE HYDROCHLORIDE) is 10 mg per day administered as divided doses of 5 mg each taken at breakfast and lunch. There is no evidence that additional benefit will be obtained from the administration of higher doses. Moreover, higher doses should ordinarily be avoided because of the increased risk of side effects.

After two to three days of selegiline treatment, an attempt may be made to reduce the dose of levodopa/carbidopa. A reduction of 10 to 30% was achieved with the typical participant in the domestic placebo controlled trials who was assigned to selegiline treatment. Further reductions of levodopa/carbidopa may be possible during continued selegiline therapy.

[AUGUST, 1990 011-25-P-103]

References:

1. Tetrud JW, Langston JW. The effect of deprenyl (selegiline) on the natural history of Parkinson's disease. *Science.* 1989;245:519–522.
2. Golbe LI, Lieberman AN, Muenter MD, et al. Deprenyl in the treatment of symptom fluctuations in advanced Parkinson's disease. *Clin Neuropharmacol.* 1988;11(1):45–55.
3. Lieberman AN, Gopinathan G, Neophytides A, et al. Deprenyl versus placebo in Parkinson's disease: A double-blind study. *NY State J Med.* 1987;87:646–649.
4. Presthus J, Hajba A. Deprenyl (selegiline) combined with levodopa and a decarboxylase inhibitor in the treatment of Parkinson's disease. *Acta Neurol Scand.* 1983;95(suppl):127–133.

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Clinical and Morphometric Analysis of the Hypoplastic Corpus Callosum

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• A total of 307 children were evaluated over a 3-year period in our neurogenetics clinic. Review of their medical records demonstrated 26 patients with diagnoses of anomalies of the corpus callosum. Morphometric analysis was performed on those 23 patients qualitatively assessed as having a hypoplastic (small, but morphologically intact) corpus callosum. Morphometric data were compared with clinical correlates for each patient. From these data, we conclude that the hypoplastic corpus callosum is not a normal variant of development but rather an indicator of a more fundamental abnormality of cerebral development.

(*Arch Neurol.* 1991;48:933-936)

The corpus callosum is the major commissural pathway between the two cerebral hemispheres. Agenesis, or complete absence, of the corpus callosum (ACC) is widely recognized as a congenital anomaly that occurs frequently in children who are evaluated for mental retardation or developmental delay. Agenesis of the corpus callosum is also often associated with other anomalies of the nervous system and anomalies of other organs.[1] Partial ACC (PACC) is also believed to be a significant malformation. It is frequently associated with developmental delay, mental retardation, infancy-onset seizures, and a large variety of congenital anomalies.[2-4] There has been no general agreement, however, about the significance of a small, but intact, corpus callosum, which we will refer to as a hypoplastic corpus callosum (HCC). Representative examples of ACC, PACC, and HCC are shown in the Figure.

One of the reasons for this lack of consensus has been that the normal range of variation of the size of corpus callosum and the change in its relative size with increasing age had not been established for nonpostmortem brains. We have recently investigated the normal range of variation in this structure and have found that there are predictable age-associated changes in its postnatal development, presumably associated with myelination.[5] Interestingly, much of this change occurs after 10 years of age. Within a given age group, however, there is relatively little variation in the size of the corpus callosum in the midsagittal plane of imaging (Table 1).

We have identified 23 children who were evaluated over a 3-year period at the Childrens' Hospital of Oklahoma, Oklahoma City, and were qualitatively assessed as having an HCC. Morphometric analysis of corpus callosum size using the magnetic resonance imaging (MRI) scans of these patients has confirmed hypoplasia in 16. Quantitative analysis of the entire midsagittal brain section and review of patient records has allowed further subdivision into those with isolated HCC (3), those with HCC associated with other anomalies (11), and those with acquired HCC (2).

PATIENTS AND METHODS

Clinical Assessment

The neurogenetics clinic at Childrens' Hospital of Oklahoma has a formal protocol for evaluation of all patients. On initial visits, all patients under 4 years of age are evaluated for developmental milestones by a certified occupational therapist with the Peabody Motor Development Scale. The standardized developmental quotient (DQ) is recorded into the patient's chart. Many of the patients over 4 years old have already had formal intelligence-education testing completed before referral. Those tests done by qualified personnel (eg, public school system, local guidance center, or licensed private psychologists or child education specialists) are not repeated. All other patients are referred to the staff child psychologist for formal, age-appropriate developmental testing. In the clinic, all children are examined by pediatric neurologists and clinical geneticists. Chromosome analysis, including fragile X studies, urine metabolic screening, and MRI of the brain are performed on all patients referred for nonspecific neurologic and/or intellectual deficits.

Patient Selection

Medical records of all patients seen in the neurogenetics clinic between 1987 and 1989 (N = 307) were reviewed. Developmental anomalies of the corpus callosum were qualitatively diagnosed on inspection of the MRI scans of 26 of these patients. Three of these were found to have complete ACC or PACC and were excluded from further study. Morphometric analyses were done on the midsagittal MRI scans of the remaining 23 patients. Results were then compared with the clinical features of each patient.

Morphometric Analysis

The T_1-weighted (repetition time, 500 to 600 ms; echo time, 20 to 30 ms) midsagittal frame of each MRI scan was measured as described by Schaefer and coworkers.[5] Slice

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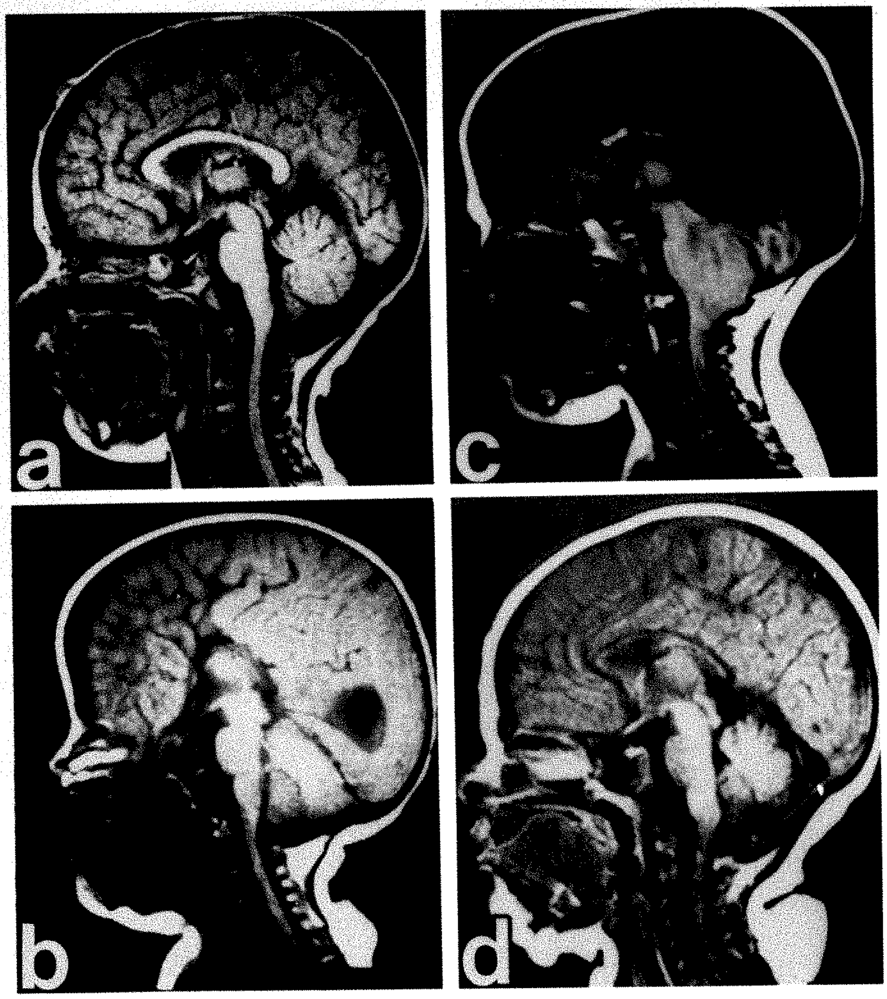

Representative T_1-weighted midsagittal magnetic resonance imaging scans of the brain illustrating a spectrum of corpus callosum development: a, normal; b, partial agenesis; c, complete agenesis; and d, hypoplasia.

thickness ranged from 5 to 9 mm, with a maximum 20% interslice gap. The field of view was 20 to 24 cm; the matrix was 128×256 or 256×256. Scans were obtained from routine clinical MRI studies that utilized superconducting magnets operated at 1.5 tesla. The standard head coil provided by each manufacturer (S15 Gyroscan, Philips, Shelton, Conn, or Signa, General Electric, Milwaukee, Wis) was used. Visualization of the entire corpus callosum, the aqueduct of Sylvius, and the fourth ventricle was used to determine the midsagittal frame. Each selected frame was photographed and printed. Cross-sectional areas of selected structures were traced and cut into pieces. These areas were measured with a simple image analysis system (Ominicon System, Bausch & Lomb, Rochester, NY).

The cross-sectional area of the corpus callosum was expressed as a ratio to the area of the total intracranial vault (TICV) cross-sectional area of the midline brain. The TICV was delineated by a line along the outer perimeter of the cerebral cortex, along the anterior surface of the brain stem to the tip of the clivus, then from the anterior to the posterior margins of the foramen magnum, and finally to the attachment of the tentorium along the inner surface of the occipital bone. The size of the corpus callosum was expressed as a ratio relative to the TICV to correct for differences in the magnification in scanning and in photographic printing. Data obtained from selected patients were compared with previously determined age-specific normative data.[5] These normative data are summarized in Table 1.

RESULTS

The clinical and morphometric features of the 23 patients qualitatively identified as having an HCC are presented in Table 2. Three of these patients (Table 2, patients 1 through 3) had HCC, apparently as an isolated anomaly. All three had DQs below 2 SDs from the norm. No dysmorphic features, birth anomalies, or focal neurologic signs were noted in any of these patients, although one has a generalized seizure disorder (patient 2). The family histories were negative for other affected relatives with significant developmental delays.

Table 1.—Normative Data on CC/TICV Ratio in Midsagittal Plane*

Age Group, y	No.	CC/TICV Mean ± SD	CC/TICV Mean − 2 SDs
≤5	20	0.034 ± 0.010	0.013
6-10	20	0.037 ± 0.007	0.023
11-15	18	0.047 ± 0.014	0.019
16-20	27	0.046 ± 0.007	0.032

*CC/TICV indicates ratio of corpus callosum area to area of total intracranial vault (as defined in the text).

An additional 11 patients (Nos. 4 through 14) had an HCC along with other developmental anomalies of the brain. Many of these anomalies involved the midline developmental field. Examples of midline anomalies seen in our patients with HCC include septo-optic dysplasia (patients 4 and 9), absent septum pellucidum (patient 4), pituitary insufficiency (patient 11), and cerebellar vermal hypoplasia or an enlarged cisterna magna as determined by quantitative analysis of MRIs compared with normative data[5,6] (patients 5, 12, and 13).

Three patients (Nos. 5, 10, and 11) had an HCC in conjunction with anomalies of organ systems other than the central nervous system. Patient 5 had facial asymmetry, bilateral cleft lip and palate, anisocoria, up-slanting palpebral fissures, posterior rotation of the ears, maxillary hypoplasia, camptodactyly of the fingers, and a seizure disorder. Patient 10 had microcephaly, dysmorphic features, esotropia, right optic atrophy, a bifid scrotum, a deep sacral dimple, unilateral transverse palmar crease, deep plantar furrows, seizures, and findings compatible with a nonspecific generalized connective tissue disorder. Patient 11 was noted to have dysmorphic features, congenital heart disease, bilateral inguinal hernias, seizures, and congenital tightness of the heel cords. Pituitary insufficiency (central growth hormone deficiency) was also present in this patient, as noted above. No known syndrome or pattern of anomalies could be defined for the constellations of anomalies seen in these patients. Each patient had normal chromosome study results. All 11 patients had a DQ more than 2 SDs below the mean.

Patients 15 and 16 were noted to have HCC with obstructive hydrocephalus. One patient (No. 16) had hydrocephalus secondary to meningomyelocele; the other (No. 15) was a child with chronic hydrocephalus due to a posterior fossa neoplasm. Interestingly, both had a normal IQ or DQ, respectively.

Seven patients (Nos. 17 through 23) qualitatively assessed as having an

Table 2.—Clinical and Morphometric Measures of Patients Qualitatively Assessed as Having HCC*

Patient No./ Age, y/Sex	CC/TICV	Clinical Features Other Than Developmental Delay or Mental Retardation
Isolated HCC		
1/1/M	0.008	. . .
2/1/F	0.014	Seizures
3/1y 6 mo/F	0.013	. . .
HCC, other anomalies		
4/1 mo/F	0.013	Septo-optic dysplasia, absent septum pellucidum
5/1 mo/F	0.002	Multiple congenital anomalies, cerebellar hypoplasia, seizures
6/2 mo/F	0.009	Meningomyelocele, colpocephaly
7/6 mo/F	0.005	Seizures, failure to thrive, microcephaly, spastic diplegia
8/7 mo/M	0.006	Idiopathic neurodegeneration
9/6 mo/M	0.013	Septo-optic dysplasia
10/1/M	0.005	Multiple congenital anomalies, microcephaly, seizures
11/2/M	0.008	Multiple congenital anomalies, syringomyelia-syringobulbia, seizures
12/4/M	0.012	Enlarged cisterna magna
13/4/F	0.004	Cerebellar hypoplasia
14/2/M	0.004	Holotelencephaly
Acquired HCC		
15/5 y 5 mo/F	0.003	Posterior fossa tumor
16/2/F	0.005	Meningomyelocele, hydrocephalus, syringomyelia
Apparent HCC (not <2 SDs)		
17/9 mo/F	0.015	. . .
18/1 y 8 mo/M	0.016	. . .
19/5/F	0.018	. . .
20/1 mo/M	0.016	Meningomyelocele
21/1/M	0.015	Enlarged cisterna magna
22/1 y 5 mo/M	0.042	Agyria
23/4/M	0.036	Enlarged cisterna magna

*HCC indicates hypoplastic corpus callosum; CC/TICV, the ratio of the corpus callosum area to the area of the total intracranial vault (as defined in the text).

HCC actually had a corpus callosum that was within 2 SDs of the normal average size for their age group (0 to 5 years old). All but two of these (patients 22 and 23) were, however, in the lower 7% of the age-corrected size range (mean ratio of corpus callosum area to TICV midline brain cross-sectional area, 0.034±0.010).

COMMENT

Agenesis of the corpus callosum, both partial and complete, is recognized as a major developmental anomaly frequently associated with functional deficits in mental ability.[7] In the past, a thin or small, but morphologically complete (hypoplastic), corpus callosum was thought to be a normal variant that could be attributed to a large degree of variability in the development of this structure. Morphometric analysis of normal individuals has now demonstrated that the size of the corpus callosum shows relatively little variation within a given age group.[5] Thus, it is possible to correlate statistically significant differences in the size of the corpus callosum with abnormalities of brain function. A preliminary accumulation of cases suggested to us that HCC is not a normal variant but, in fact, a significant finding suggestive of more global aberrant brain development.[8]

We initiated this study to investigate this issue further. A retrospective review was performed on all cases seen in our neurogenetics clinic over a 3-year period. Of the 307 patients seen during this period, three (1.0%) were noted to have complete ACC or PACC. This finding is comparable with the range of 0.2% to 2.9% found in other studies that have looked for these callosal anomalies in patient populations selected for developmental delays or mental retardation.[7,9]

We identified an additional 23 patients qualitatively assessed as having an HCC. This was confirmed by morphometric analysis in 16 (5.2% of the total sample). Anomalies of the corpus callosum, in general, thus represented a significant proportion (6%) of patients in our population, a population selected for developmental delays. We found no sex, race, or socioeconomic predilection in our patients with callosal anomalies.

All 16 patients with an HCC had mental retardation (DQ or IQ <2 SDs below the mean), with the exception of two patients (Nos. 15 and 16). Both of these patients were noted to have hydrocephalus, one associated with meningomyelocele and the other with a posterior fossa neoplasm. The occurrence of normal intellect with an HCC in these two patients is consistent with a mechanical postnatal thinning of this structure. Thus, in these cases, the small size of the corpus callosum would be a secondary phenomenon rather than an indicator of primary cerebral dysgenesis. This "secondary HCC" may be analogous to the HCC noted by Barkovich and Norman[4] in patients with cerebral palsy. In our patients, however, only one (patient 7) had a clinical picture suggestive of cerebral palsy. We would interpret these findings to suggest that, in the absence of indicators of factors that could influence callosal size after primary morphogenesis, HCC is an indicator of aberrant cerebral development.

The majority of patients with HCC (80%) had other developmental anomalies of the brain. Many of these anomalies were defects in midline structures, eg, hypoplasia of the cerebellar vermis, septo-optic dysplasia, absence of the septum pellucidum, pituitary insufficiency, or an enlarged cisterna magna. (A large cisterna magna is commonly classified as a "normal variant." However, we believe that it is not a normal variant but rather an extension of the spectrum of midline brain defects.[10] We will include it as such for purposes of discussion in this article.) The other nervous system anomalies seen in our patients with HCC largely included more generalized defects such as agyria, colpocephaly, holotelencephaly, and syringomyelia-syringobulbia.

Three patients had multiple congenital anomalies of organ systems other than the central nervous system. It is well recognized that patients with ACC and PACC have an increased incidence of anomalies outside of the central nervous system. Ocular, craniofacial, musculoskeletal, and cardiovascular are the most commonly reported associated anomalies.[1,4,11] The associated anomalies seen in our patients with HCC as detailed above are strikingly similar to those reported for ACC and PACC. The overall incidence of associated anomalies seen in our patients (3/16 [19%]) is also consistent with that reported for ACC and PACC. Further studies will be needed to determine if the scope and magnitude of associated anomalies in HCC are truly comparable with those seen in ACC and PACC.

In this study, we limited our analysis

of MRI scans to the T_1-weighted midsagittal slice. We acknowledge that there may be abnormalities of the corpus callosum that are not seen in the midline or not appreciated on T_1-weighted images. Thus, our estimate of the frequency of anomalies of the corpus callosum in patients with nonspecific mental retardation may be an underestimate. The advantage of limiting analysis to the midline is that it greatly simplifies the method (eg, complex volumetric measurements are avoided), which makes the technique more easily accessible to the clinician. Even though conservative, this type of analysis is likely to identify a large proportion of patients with abnormal events in brain development and to provide information that is of interest to the clinician.

We interpret these data to indicate that HCC is not a normal variant. Instead, HCC appears to be an indicator of a more fundamental abnormality of cerebral development. Furthermore, while no characteristic clinical neurologic syndrome can be identified in these patients, HCC is usually associated with subnormal intellectual function variable degree. Morphometric data helpful in providing objective measu of callosal size for correlation with t level of intellectual function. The in dence of this anomaly is unknown fo normative control group, but it is a re tively frequent anomaly in populati selected for developmental delay mental retardation.

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We thank Coral McCallister for the illustratio

References

1. Parrish ML, Roessmann U, Levinsohn MW. Agenesis of the corpus callosum: a study of the frequency of associated malformations. *Ann Neurol.* 1979;6:349-354.

2. Lacey DJ. Agenesis of the corpus callosum. *AJDC.* 1985;139:953-955.

3. McLeod NA, Williams JP, Machen B, Lum GB. Normal and abnormal morphology of the corpus callosum. *Neurology.* 1987;37:1240-1242.

4. Barkovich SA, Norman D. Anomalies of the corpus callosum: correlation with further anomalies of the brain. *Am J Neuroradiol.* 1988;9:493-501.

5. Schaefer GB, Thompson JN Jr, Bodensteiner JB, et al. Quantitative morphometric analysis of brain growth using magnetic resonance imaging. *J Child Neurol.* 1990;5:127-130.

6. Schaefer GB, Thompson JN Jr, Bodensteiner JB, Gingold M, Wilson M, Wilson D. Age-related changes in the relative growth of the posterior fossa. *J Child Neurol.* 1991;6:15-19.

7. Aicardi J, Chevrie JJ, Baraton J. Agenesis of the corpus callosum. In: Vinken PJ, Bruyn GW, Klawans HL, Myrianthopoulos NC, eds. *Handbook of Clinical Neurology.* New York, NY: Elsevier Science Publishing Co Inc; 1987;50:149-173.

8. Bodensteiner JB, Schaefer GB, Thompson J, et al. Clinical and morphometric analysis of the hypoplastic corpus callosum. *Ann Neurol.* 1988;24:355. Abstract.

9. Jeret JS, Serur D, Wisniewski K, Fisch Frequency of agenesis of the corpus callosum in developmentally disabled population as de mined by computed tomography. *Pediatr N rosci.* 1985-1986;12:101-103.

10. Bodensteiner J, Gay C, Marks W, Hamza Schaefer GB. The macro cisterna magna: a mar for maldevelopment of the brain? *Pediatr Neu* 1988;4:284-286.

11. Jeret JS, Serur D, Wisniewski KE, Lu RA. Clinicopathological findings associated agenesis of the corpus callosum. *Brain* 1987;9:255-264.

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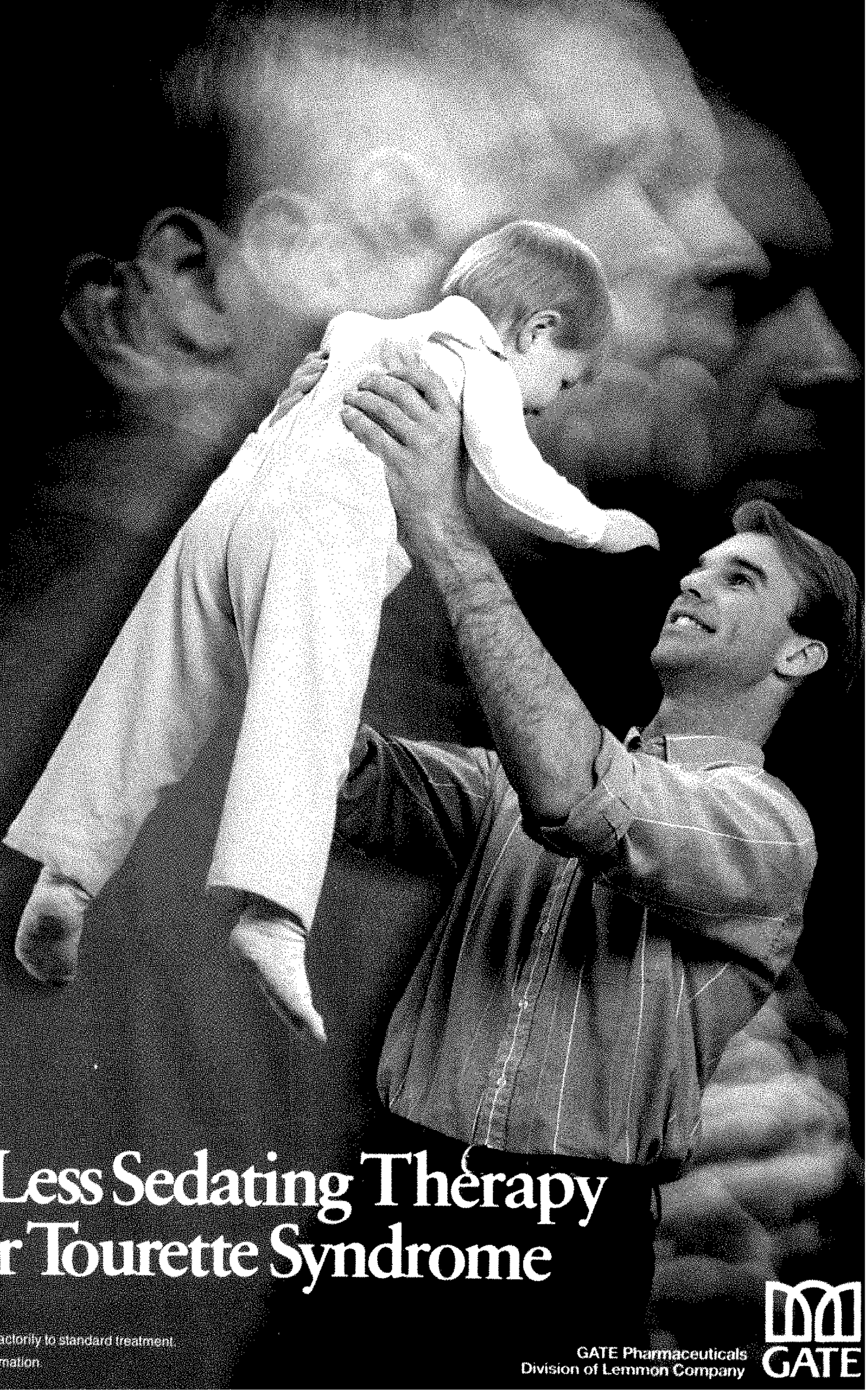

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INDICATIONS AND USAGE

ORAP (pimozide) is indicated for the suppression of motor and phonic tics in patients with Tourette's Disorder who have failed to respond satisfactorily to standard treatment. ORAP is not intended as a treatment of first choice nor is it intended for the treatment for tics that are merely annoying or cosmetically troublesome. ORAP should be reserved for use in Tourette's Disorder patients whose development and/or daily life function is severely compromised by the presence of motor and phonic tics.

Evidence supporting approval of pimozide for use in Tourette's Disorder was obtained in two controlled clinical investigations which enrolled patients between the ages of 8 and 53 years. Most subjects in the two trials were 12 or older.

CONTRAINDICATIONS

1. ORAP (pimozide) is contraindicated in the treatment of simple tics or tics other than associated with Tourette's Disorder.
2. ORAP should not be used in patients taking drugs that may, themselves, cause motor and phonic tics (e.g., pemoline, methylphenidate and amphetamines) until such patients have been withdrawn from these drugs to determine whether or not the drugs, rather than Tourette's Disorder, are responsible for the tics.
3. Because ORAP prolongs the QT interval of the electrocardiogram it is contraindicated in patients with congenital long QT syndrome, patients with a history of cardiac arrhythmias, or patients taking other drugs which prolong the QT interval of the electrocardiogram (see DRUG INTERACTIONS).
4. ORAP is contraindicated in patients with severe toxic central nervous system depression or comatose states from any cause.
5. ORAP is contraindicated in patients with hypersensitivity to it. As it is not known whether cross-sensitivity exists among the antipsychotics, pimozide should be used with appropriate caution in patients who have demonstrated hypersensitivity to other antipsychotic drugs.

WARNINGS

The use of ORAP (pimozide) in the treatment of Tourette's Disorder involves different risk/benefit considerations than when antipsychotic drugs are used to treat other conditions. Consequently, a decision to use ORAP should take into consideration the following: (see also PRECAUTIONS–Information for Patients).

Tardive Dyskinesia A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to antipsychotic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS and PRECAUTIONS–Information for Patients.)

Neuroleptic Malignant Syndrome (NMS) A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs) and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmias). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Hyperpyrexia, not associated with the above symptom complex, has been reported with other antipsychotic drugs.

Other Sudden, unexpected deaths have occurred in experimental studies of conditions other than Tourette's Disorder. These deaths occurred while patients were receiving dosages in the range of 1 mg per kg. One possible mechanism for such deaths is prolongation of the QT interval predisposing patients to ventricular arrhythmia. An electrocardiogram should be performed before ORAP treatment is initiated and periodically thereafter, especially during the period of dose adjustment.

ORAP may have a tumorigenic potential. Based on studies conducted in mice, it is known that pimozide can produce a dose related increase in pituitary tumors. The full significance of this finding is not known, but should be taken into consideration in the physician's and patient's decisions to use this drug product. This finding should be given special consideration when the patient is young and chronic use of pimozide is anticipated. (see PRECAUTIONS–Carcinogenesis, Mutagenesis, Impairment of Fertility).

PRECAUTIONS

General ORAP (pimozide) may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks, such as driving a car or operating machinery, especially during the first few days of therapy.

ORAP produces anticholinergic side effects and should be used with caution in individuals whose conditions may be aggravated by anticholinergic activity.

ORAP should be administered cautiously to patients with impairment of liver or kidney function, because it is metabolized by the liver and excreted by the kidneys.

Antipsychotics should be administered with caution to patients receiving anticonvulsant medication, with a history of seizures, or with EEG abnormalities, because they may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be maintained concomitantly.

Laboratory Tests An ECG should be done at baseline and periodically thereafter throughout the period of dose adjustment. Any indication of prolongation of QT_c interval beyond an absolute limit of 0.47 seconds (children) or 0.52 seconds (adults), or more than 25% above the patient's original baseline should be considered a basis for stopping further dose increase (see CONTRAINDICATIONS) and considering a lower dose.

Since hypokalemia has been associated with ventricular arrhythmias, potassium insufficiency, secondary to diuretics, diarrhea, or other cause, should be corrected before ORAP therapy is initiated and normal potassium maintained during therapy.

Drug Interactions Because ORAP prolongs the QT interval of the electrocardiogram, an additive effect on QT interval would be anticipated if administered with other drugs, such as phenothiazines, tricyclic antidepressants or antiarrhythmic agents, which prolong the QT interval. Such concomitant administration should not be undertaken (see CONTRAINDICATIONS).

ORAP may be capable of potentiating CNS depressants, including analgesics, sedatives, anxiolytics, and alcohol

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenicity studies were conducted in mice and rats. In mice, pimozide causes a dose-related increase in pituitary and mammary tumors.

When mice were treated for up to 18 months with pimozide, pituitary gland changes developed in females only. These changes were characterized as hyperplasia at doses approximating the human dose and adenoma at doses about fifteen times the maximum recommended human dose on a mg per kg basis. The mechanism for the induction of pituitary tumors in mice is not known

Mammary gland tumors in female mice were also increased, but these tumors are expected in rodents treated with antipsychotic drugs which elevate prolactin levels. Chronic administration of an antipsychotic also causes elevated prolactin levels in humans. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with antipsychotic drugs, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis. The available evidence, however, is considered too limited to be conclusive at this time.

In a 24 month carcinogenicity study in rats, animals received up to 50 times the maximum recommended human dose. No increased incidence of overall tumors or tumors at any site was observed in either sex. Because of the limited number of animals surviving this study, the meaning of these results is unclear.

Pimozide did not have mutagenic activity in the Ames test with four bacterial test strains, in the mouse dominant lethal test or in the micronucleus test in rats.

Reproduction studies in animals were not adequate to assess all aspects of fertility. Nevertheless, female rats administered pimozide had prolonged estrus cycles, an effect also produced by other antipsychotic drugs.

Pregnancy Category C. Reproduction studies performed in rats and rabbits at oral doses up to 8 times the maximum human dose did not reveal evidence of teratogenicity. In the rat, however, this multiple of the human dose resulted in decreased pregnancies and in the retarded development of fetuses. These effects are thought to be due to an inhibition or delay in implantation which is also observed in rodents administered other antipsychotic drugs. In the rabbit, maternal toxicity, mortality, decreased weight gain, and embryotoxicity including increased resorptions were dose related. Because animal reproduction studies are not always predictive of human response, pimozide should be given to a pregnant woman only if the potential benefits of treatment clearly outweigh the potential risks

Labor and Delivery This drug has no recognized use in labor or delivery.

Nursing Mothers It is not known whether pimozide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for tumorigenicity and unknown cardiovascular effects in the infant, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use Although Tourette's Disorder most often has its onset between the ages of 2 and 15 years, information on the use and efficacy of ORAP in patients less than 12 years of age is limited.

Because its use and safety have not been evaluated in other childhood disorders, ORAP is not recommended for use in any condition other than Tourette's Disorder.

ADVERSE REACTIONS

General: Extrapyramidal Reactions. Neuromuscular (extrapyramidal) reactions during the administration of ORAP (pimozide) have been reported frequently, often during the first few days of treatment. In most patients, these reactions involved Parkinson-like symptoms which, when first observed, were usually mild to moderately severe and usually reversible.

Other types of neuromuscular reactions (motor restlessness, dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently. Severe extrapyramidal reactions have been reported to occur at relatively low doses. Generally the occurrence and severity of most extrapyramidal symptoms are dose related since they occur at relatively high doses and have been shown to disappear or become less severe when the dose is reduced. Administration of antiparkinson drugs such as benztropine mesylate or trihexyphenidyl hydrochloride may be required for control of such reactions. It should be noted that persistent extrapyramidal reactions have been reported and that the drug may have to be discontinued in such cases.

Withdrawal Emergent Neurological Signs: Generally, patients receiving short term therapy experience no problems with abrupt discontinuation of antipsychotic drugs. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain of these cases the dyskinetic movements are indistinguishable from the syndrome described below under 'Tardive Dyskinesia' except for duration. It is not known whether gradual withdrawal of antipsychotic drugs will reduce the rate of occurrence of withdrawal emergent neurological signs but until further evidence becomes available, it seems reasonable to gradually withdraw use of ORAP.

Tardive Dyskinesia: ORAP may be associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk.

There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked.

It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop.

Electrocardiographic Changes: Electrocardiographic changes have been observed in clinical trials of ORAP in Tourette's Disorder and schizophrenia. These have included prolongation of the QT interval, flattening, notching and inversion of the T wave and the appearance of U waves. Sudden, unexpected deaths and grand mal seizure have occurred at doses above 20 mg/day

Neuroleptic Malignant Syndrome: Neuroleptic malignant syndrome (NMS) has been reported with ORAP. (See WARNINGS for further information concerning NMS.)

Hyperpyrexia: Hyperpyrexia has been reported with other antipsychotic drugs.

Clinical Trials The following adverse reaction tabulation was derived from 20 patients in a 6 week long placebo controlled clinical trial of ORAP in Tourette's Disorder.

Body System/ Adverse Reaction	Pimozide (N = 20)	Placebo (N = 20)
Body as a Whole		
Headache	1	2
Gastrointestinal		
Dry mouth	5	1
Diarrhea	1	0
Nausea	0	2
Vomiting	0	1
Constipation	4	2
Eructations	0	1
Thirsty	1	0
Appetite increase	1	0
Endocrine		
Menstrual disorder	0	1
Breast secretions	0	1
Musculoskeletal		
Muscle cramps	0	1
Muscle tightness	3	0
Stooped posture	2	0
CNS		
Drowsiness	7	3
Sedation	14	5
Insomnia	2	2
Dizziness	0	1
Akathisia	8	0
Rigidity	2	0
Speech disorder	2	0
Handwriting change	1	0
Akinesia	8	0
Psychiatric		
Depression	2	3
Excitement	0	1
Nervous	1	0
Adverse behavior effect	5	0
Special Sense		
Visual disturbance	4	0
Taste change	1	0
Sensitivity of eyes to light	1	0
Decreased accommodation	4	1
Spots before eyes	0	1
Urogenital		
Impotence	3	0

Because clinical investigational experience with ORAP in Tourette's Disorder is limited, uncommon adverse reactions may not have been detected. The physician should consider that other adverse reactions associated with antipsychotics may occur.

Other Adverse Reactions In addition to the adverse reactions listed above, those listed below have been reported in U.S. clinical trials of ORAP in conditions other than Tourette's Disorder.

Body as a Whole: Asthenia, chest pain, periorbital edema
Cardiovascular/Respiratory: Postural hypotension, hypotension, hypertension, tachycardia, palpitations
Gastrointestinal: Increased salivation, nausea, vomiting, anorexia, GI distress
Endocrine: Loss of libido
Metabolic/Nutritional: Weight gain, weight loss
Central Nervous System: Dizziness, tremor, parkinsonism, fainting, dyskinesia
Psychiatric: Excitement
Skin: Rash, sweating, skin irritation
Special Senses: Blurred vision, cataracts
Urogenital: Nocturia, urinary frequency

Postmarketing Reports The following experiences were described in spontaneous postmarketing reports. These reports do not provide sufficient information to establish a clear causal relationship with the use of ORAP.

Hematologic: Hemolytic anemia

OVERDOSAGE

In general, the signs and symptoms of overdosage with ORAP (pimozide) would be an exaggeration of known pharmacologic effects and adverse reactions, the most prominent of which would be: 1) electrocardiographic abnormalities, 2) severe extrapyramidal reactions, 3) hypotension, 4) a comatose state with respiratory depression.

In the event of overdosage, gastric lavage, establishment of a patent airway and, if necessary mechanically-assisted respiration are advised. Electrocardiographic monitoring should commence immediately and continue until the ECG parameters are within the normal range. Hypotension and circulatory collapse may be counteracted by use of intravenous fluids, plasma, or concentrated albumin, and vasopressor agents such as metaraminol, phenylephrine and norepinephrine. Epinephrine should not be used. In case of severe extrapyramidal reactions, antiparkinson medication should be administered. Because of the long half-life of pimozide, patients who take an overdose should be observed for at least 4 days. As with all drugs, the physician should consider contacting a poison control center for additional information on the treatment of overdose

DOSAGE AND ADMINISTRATION

Reliable dose response data for the effects of ORAP (pimozide) on tic manifestations in Tourette's Disorder patients below the age of twelve are not available. Consequently, the suppression of tics by ORAP requires a slow and gradual introduction of the drug. The patient's dose should be carefully adjusted to a point where the suppression of tics and the relief afforded is balanced against the untoward side effects of the drug.

An ECG should be done at baseline and periodically thereafter, especially during the period of dose adjustment (see WARNINGS and PRECAUTIONS–Laboratory Tests).

In general, treatment with ORAP should be initiated with a dose of 1 to 2 mg a day in divided doses. The dose may be increased thereafter every other day. Most patients are maintained at less than 0.2 mg/kg per day, or 10 mg/day, whichever is less. Doses greater than 0.2 mg/kg/day or 10 mg/day are not recommended.

Periodic attempts should be made to reduce the dosage of ORAP to see whether or not tics persist at the level and extent first identified. In attempts to reduce the dosage of ORAP, consideration should be given to the possibility that increases of tic intensity and frequency may represent a transient, withdrawal related phenomenon rather than a return of disease symptoms. Specifically, one to two weeks should be allowed to elapse before one concludes that an increase in tic manifestations is a function of the underlying disease syndrome rather than a response to drug withdrawal. A gradual withdrawal is recommended in any case.

HOW SUPPLIED

ORAP (pimozide) 2 mg tablets, white, scored, imprint "LEMMON" and "ORAP-2"—NDC 57844-187-01, bottles of 100.

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1. Shapiro AK et al: *Pediatrics* 79:1032-1038, 1987.
2. Ross MS et al: *Am J Psychiatry* 135:585-587, 1978.

Alcohol-Induced Brain Changes in Dogs

Lawrence A. Hansen, MD; Benjamin H. Natelson, MD; Cynthia Lemere, MS; Wendell Niemann, DVM;
Richard De Teresa; Timothy J. Regan, MD; Eliezer Masliah, MD; Robert D. Terry, MD

• We studied the neuropathologic effects of chronic alcohol ingestion on the brains of healthy, well-nourished, male mongrel dogs. Five experimental dogs were provided 36% of their calories as ethyl alcohol for 1 year. Following killing, their brains were weighed, photographed, sectioned, and processed for computerized morphometric determinations of ventricular size, cortical thickness, and neocortical neuron and glial cell populations. Compared with a similarly handled control group, the alcoholic dog brains showed lateral ventricular enlargement, cortical thinning in the temporal lobe only, and fewer glial cells in the temporal and frontal cortices. There were no statistically significant differences between the alcoholic and control groups in brain weight, frontal or parietal cortical thickness, or neocortical neuron populations. These results imply a disproportionate vulnerability of white matter to the damaging effects of alcohol with consequent lateral ventricular enlargement, and some regional variation in neocortical susceptibility to alcohol-induced cortical thinning and glial cell loss. In general, such changes are consistent with those described in neuroradiologic imaging studies of human alcoholics.

(*Arch Neurol*. 1991;48:939-942)

Every neurologist is aware of an association between alcoholism and mental function, and indeed a recent review of causes of dementia notes that alcoholism is diagnosed as the etiologic factor in 7% of all demented patients.[1] Supporting the idea of an association between alcoholism and brain disease are several radiologic[2] and pathologic[3-5] studies that show hydrocephalus and brain shrinkage by computed tomography in alcoholic patients.

Unfortunately, such studies do not allow one to decide whether the relationship between alcoholism and cognitive dysfunction is merely associative or whether the relationship is one of cause and effect. After all, it is known that alcoholics have a number of other major risk factors, which can summate as clinical dementia. These include (1) poor nutrition that can produce Wernicke-Korsakoff syndrome, (2) repeated head trauma related directly or indirectly to drinking that can produce the punch drunk syndrome, and (3) repeated seizures (ie, alcohol withdrawal seizures or rum fits) that can produce head trauma and/or cerebral anoxia.

Harper et al[6] have collected additional neuropathologic data from humans in an effort to clarify the question of what alcohol does to the brain. They showed that frank alcoholism was associated with significantly larger ventricular volume than control subjects drinking less than 20 g of ethyl alcohol per day. Importantly, moderate drinkers, those drinking 30 to 80 g per day, had ventricular volumes that were intermediate between those of the control subjects and those of the alcoholics. This study suggests that alcohol may be a primary cerebrotoxin. However, the classification of "moderate" or "alcoholic" was always done retrospectively, and so one can never be sure about the patient's drinking status.

Unfortunately, in understanding the cause of any human disease, research with humans rarely allows one to go definitively beyond associations among variables to cause-and-effect relationships. One way to circumvent this problem is to use animal models—a tactic we have chosen. This allows one to eliminate extraneous causes of brain disease by controlling dietary and medical conditions in experimental animals.

In this study, we used 2- to 3-year-old healthy male mongrel dogs to assess the neuropathologic effects of a high alcohol diet in an experimental group consuming 36% of their daily calories as ethyl alcohol. The brains of the alcoholic and control dogs were fixed, sectioned, photographed, and examined with computerized morphometric methods to determine ventricular sizes and neocortical neuron and glial populations in various lobes. Since the experimental alcoholic and control dogs were fed calorically similar diets and maintained under identical conditions, any neuropathologic changes found could be attributed to the effects of alcohol rather than to nutritional deficiencies. We obtained results generally comparable with those found using neuroradiologic imaging techniques in the analysis of human alcoholic brains, ie, ventricular enlargement presumably caused by reduced white matter volume and comparatively subtle neocortical alterations.

MATERIALS AND METHODS

Male mongrel dogs, 2 to 3 years of age, were selected from animals in good health and divided into control and chronic ethyl alcohol groups. The dogs in the two groups were matched well for size, with those in the alcohol group having weights ranging from 25.3 to 32.0 kg (mean, 28.6 kg), and with those in the control group having weights ranging from 22.0 to 32.0 kg (mean, 26.7 kg).

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All were vaccinated against distemper, hepatitis, and leptospirosis, and were housed in individual cages. They were free of intestinal parasites and clinical evidence of disease for a period of 6 to 8 weeks of observation before admission to the study. Blood samples were negative for heartworms, and both hematocrit and serum protein levels were initially normal. The control dogs received a diet sufficient to maintain body weight in the adult animals (260.4 J/kg), consisting of 26% of calories as protein, 12% fat, and 62% carbohydrate. The corresponding values in the alcoholic group were 16.6% of calories as protein, 7.7% lipid, and 39.7% carbohydrate, which met the minimum standard for maintaining a normal nutritional state.[7]

After 4 weeks of progressively increasing doses, animals consuming virtually all the ethyl alcohol provided were admitted to the experimental group. There were five dogs in the control group and five in the alcohol group. The chronic ethyl alcohol animals were provided 36% of calories as ethyl alcohol for 6 days per week. On the seventh day, the nonalcoholic control diet was provided. Due to difficulties in feeding by gastric tube for prolonged periods, the ethyl alcohol (USP, US Industrial Chemicals, Division of National Distillers and Chemical Corp, New York, NY) was administered with the food. Apart from obvious sedation related to the alcohol meal, the experimental animal could not be differentiated from the control dogs. After 11 to 12 months the animals were anesthetized with chloralose following an overnight fast. Electrophysiologic and metabolic studies were performed over the subsequent 3 hours, while these closed-chest animals were ventilated through an endotracheal tube with 40% oxygen. Blood was collected for assay of hematocrit, albumin, and electrolyte concentrations. In terms of these blood indexes, good nutrition was documented in the alcohol-fed group, since mean values for albumin, sodium, potassium, chloride, and hematocrit did not differ significantly from those of the control dogs. At termination the chest was opened, and the heart was arrested with iced Ringer's solution. Both common carotids were clamped, cannulated, chilled, heparinized, and perfused with saline followed by formaldehyde solution. The calvarium was then opened and the brain removed and stored in 4% formaldehyde solution for several months.

The brains were then photographed and weighed both with and without the brain stems and cerebellums attached. Tissue blocks for neocortical morphometry were taken from the left hemisphere. The frontal lobe section was from the pars anterior of the sigmoid gyrus in the precoronal region, the territory of the motor cortex. The temporal lobe section was from the pars posterior of the sylvian gyrus, posterior to the sylvian fissure. The parietal lobe section was from the junction of the gyrus suprasylvius medium and gyrus suprasylvius posterior.[8] It can be contended, on cytoarchitectural criteria, that this brain region is actually a part of the temporal lobe rather than the parietal lobe. We chose this area, nevertheless, because on gross inspection of the lateral surface of the brain it most closely corresponded to the inferior parietal lobule in the human brain. In selecting these three neocortex sections for analysis, we were attempting to parallel those used in morphometric studies of the human brain concerning normal aging, Alzheimer's disease, and alcoholism. Specifically, the brain regions analyzed in those investigations are the midfrontal cortex, superior temporal gyrus, and inferior parietal area.

Two coronal slices were made to evaluate the cross-sectional areas of the ventricular systems. The anterior section was made through the temporal tips, perpendicular to the long fronto-occipital axis of the specimen. The posterior level was made at or near the splenium of the corpus callosum. To evaluate the size of the fourth ventricle, a section was taken through the pontomesencephalic junction at the level of the genu of the facial nerve. Using a computerized image analysis system (Quantimet 970), the black-and-white photographs of the brain slices were digitized into computer images, allowing measurement of ventricular areas at the three levels.

Tissue blocks taken from frontal, temporal, and parietal lobes were oriented carefully to ensure that the cortex along the sulcus was cut perpendicular to the pial surface. Following paraffin embedding, 20-μm-thick cresyl violet preparations were made. Counts were performed with the computerized image analysis system in a rectangle of cortex measuring 360 μm in width along the pial surface extending through the full cortical thickness. The microscopic image was visualized on a video screen that allowed manual editing of the computer image. Contiguous cells were separated, vascular elements and artifacts were excluded, and cells whose cytoplasmic outlines were incompletely detected (by the computerized counting program) were filled in before measurement.

All cresyl violet-stained cells in the neocortex were classified into size groups according to the areas of the perikarya in square microns. To determine which cells were neurons and which cells were glia, we performed the following analysis using both alcoholic and normal control dog brain sections from the frontal and parietal lobes. Moving from the pial surface to the white matter through the counted neocortical area, all cells that could be definitely identified as neurons on the basis of nuclear morphology, nucleolar prominence, Nissl substance, and pyramidal shape were measured and counted. The same cortical area was then counted again, only this time those cells that could be definitely identified as either astrocytes or oligodendroglia were measured and counted. Morphologic criteria for these decisions were nuclear shape, chromatin pattern, and cytoplasmic contours. These determinations were performed in four cases (two normal subjects and two alcoholics) for both neurons and glia. We found that 98% of all cells that could be definitively identified as neurons were 80 μm^2 or greater in cross-sectional area, while 99% of all cells definitively identifiable as glia were less than 80 μm^2, and 95% of these were less than 60 μm^2. There was, therefore, almost no overlap between neurons and glia, and cell size/cell type correlations could be made with confidence. We made a similar attempt to distinguish between oligodendroglia and astrocytes on the basis of cross-sectional area. Despite the fact that oligodendroglia were, on average, smaller than astrocytes, these two cell types showed too much size overlapping to allow confident distinction between them based on cell surface area. For the purposes of this study, we therefore lumped oligodendroglia, astrocytes, and microglia in the single category of glial cells.

RESULTS

Statistical comparisons between data from alcoholics and controls were made by averaging the measured variables for each group and using the two-tailed Student *t* test. Significance was assigned if the *P* value was less than .05. The results are given in Tables 1 and 2. Significant differences between alcoholic and control brains were found in only five of 16 measured variables. Compared with the control brains, the alcoholic specimens had larger lateral ventricles and cerebral aqueducts, a thinner cortical ribbon in the temporal section only, and fewer glial cells in the temporal and frontal cortices. The ventricular enlargement was most prominent posteriorly, at the level of the splenium of the corpus callosum (Figure). Lateral ventricle surface areas in four of five alcoholic dogs exceeded the mean lateral ventricle size for the five control dogs by more than 1 SD. There were no statistically significant differences in whole brain weights, cerebral weights, or the weights of the combined brain stem and cerebellum. There was no difference in frontal or parietal cortical thickness, and neuron populations in all neocortical regions were undiminished in the alcoholic group. We did not compare mean neuron sizes in the two groups. There was no statistically significant enlargement of the third or fourth ventricles in the alcoholic compared with control brains, and glial populations in the parietal section were the same.

COMMENT

To our knowledge, this study is the first to show definitively that alcohol can directly harm the brain and thus conceivably produce dementia. These results imply that white matter rather than gray matter bears the brunt of the neuropathologic damage caused by high alcohol intake. Neuron populations from all neocortical regions were undiminished in the alcoholic compared with the control brains, and the cortex showed significant thinning only in the temporal lobe. However, the lateral ventricles and cerebral aqueduct were dilated, and this must be interpreted as reflecting reduced white matter volume, since the cortex showed only slight regional thinning. Interestingly, there is an apparent loss of glial cells (either astrocytes or oligodendroglia) in both the frontal and temporal cortices.

These data in a nonhuman animal model confirm the findings of many neuroradiologic and morphometric studies of alcoholic human brains. Some investigators have found diminished brain weights among alcoholics,[9] but others have found no significant diminution in mean brain weight compared with controls.[5] Brain weights did not differ significantly in our study between the alcoholics and the control group. Many investigators have found disproportionate atrophy of cerebral white matter compared with gray matter among alcoholics.[3-5,9-12]

Our finding of greater temporal lobe changes (cortical thinning and loss of glial cells) also supports the concept of regional variation in the severity of neuropathologic effects of alcohol. It has long been known that alcohol causes neuron loss in the rostral cerebellar vermis while leaving other regions of cerebellum relatively unaffected. Similarly, quantitative morphometric studies of human alcoholic brains have shown some neuron loss in the superior frontal cortex, while neuron populations were undiminished in the motor cortex.[4] Nevertheless—at least over the time span of alcohol exposure used in this study—nerve cell loss per se does not appear to be a major pathologic effect of alcohol. Rather, neuronal shrinkage could occur while the white matter volume is diminishing. We are unable to comment on neuronal shrinkage as such, since our computer program serves to measure cells and assign them to size categories, but not to determine average cell sizes within those categories. Absence of irreversible cell loss secondary to alcohol consumption is, however, supported by many studies showing reversibility, both of ventricular enlargement and of deficits in psychologic testing evidenced by alcoholics.[11]

Table 1.—Mean Brain Weights and Ventricular Sizes*

	Control Subjects (SD) (N = 5)	Alcoholics (SD) (N = 5)	P
Whole brain weights, g	102 (15.7)	94.2 (7.53)	NS
Cerebral weights, g	85 (14.3)	78.6 (6.95)	NS
Brain stem / cerebellum, mm^2	16.8 (1.92)	15.6 (0.89)	NS
Lateral ventricles, mm^2	134 (59.1)	234 (56.4)	<.05
Third ventricle, mm^2	5.5 (1.74)	8.82 (4.12)	NS
Aqueduct of Silvius, mm^2	4.4 (0.97)	6.08 (0.99)	<.05
Fourth ventricle, mm^2	44.8 (18.8)	27.8 (2.88)	NS

*NS indicates not significant.

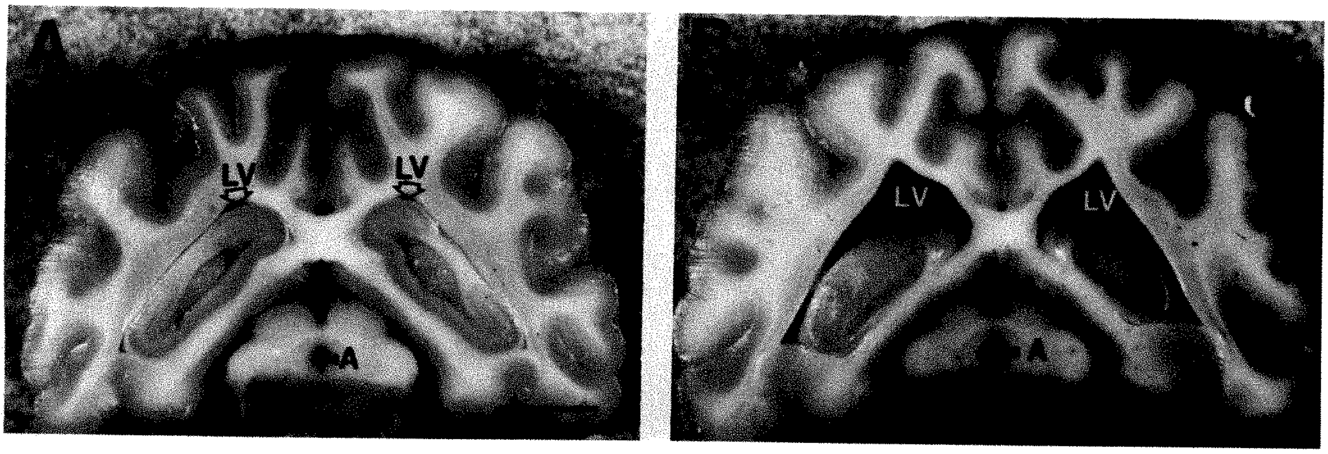
Table 2.—Neocortical Morphometry*

	Control Subjects (SD) (N = 5)	Alcoholics (SD) (N = 5)	P
Mean cortical thicknesses, μm			
Frontal	1930 (274)	1800 (177)	NS
Temporal	2130 (239)	1730 (228)	<.05
Parietal	1730 (141)	1690 (123)	NS
Mean neuron counts			
Frontal	316 (92)	298 (38)	NS
Temporal	355 (71)	291 (27)	NS
Parietal	362 (53)	371 (49)	NS
Mean glia counts			
Frontal	722 (94)	586 (76)	<.05
Temporal	678 (183)	440 (37)	<.05
Parietal	730 (124)	724 (229)	NS

*Neurons are all cells 80 μm^2 or larger; glia are all cells less than 80 μm^2; NS indicates not significant.

The cause of reduced white matter volume is speculative. If axons shrink in response to chronic alcohol ingestion, loss of axonal caliber may be accompanied by thinning of myelin sheaths and resulting white matter shrinkage. Alternatively, our finding of diminished glial cells in the neocortex may reflect damage to oligodendroglia, and suggests that these cells may be affected directly in the underlying white matter. Experimental models of ethyl alcohol-induced neurotoxicity have shown abnormal myelin development in rats exposed to alcohol in utero, with delayed myelination and reduced accumulation of brain myelin.[13] Alcohol consumption in the first two trimesters increases the risk of producing children

Representative brains from the control group (left) and the alcoholic group (right). At the level of the splenium of the corpus callosum, both the lateral ventricles and the cerebral aqueduct were enlarged in the alcoholics. LV indicates lateral ventricles; A, aqueduct.



whose development is delayed and growth lags permanently. Alcohol in the third trimester and during lactation may increase the risk of impaired normal development of brain myelin. A study of alcoholic brains in patients without Wernicke's disease showed diminished myelin in the mamillary bodies compared with controls, but normal amounts of myelin in dorsal thalamus, quadrigeminal plate, and cerebellar vermis. These data were interpreted as reflecting regional variation in susceptibility to alcohol damage and as implying a specific myelin vulnerability.[14] Further support for the concept of alcohol myelin toxicity comes from a study showing delayed latencies of auditory brain-stem potentials in alcoholics compared with controls. These findings were considered suggestive of possible demyelination of auditory tracts in alcoholics.[15] Simple dehydration in alcoholism as an explanation for the white matter loss does not seem to be an operative mechanism. In fact, neurochemical studies of white matter in alcoholics have shown decreased lipid content and increased water content.[6] White matter is about 70% water, 20% lipid, and 10% protein, and most of the lipid and protein are combined to form membranes, myelin in particular. When the water content increases the lipid content decreases, and this pattern of change can be seen in both demyelinating conditions and wallerian degeneration.[6] The increased white matter water content in alcoholics could be due either to axonal loss (wallerian degeneration) or to more subtle primary myelin alterations. Whether the neurotoxic effects of alcohol in the centrum semiovalae are attributable to damage to axons primarily or oligodendroglial cells is presently undetermined.

Further studies using this dog model would be necessary to determine if the alcohol-induced ventricular dilatation is reversible by abstinence. Nevertheless, the otherwise relatively mild effects of high alcohol intake seen in this study as well as the reversibility of the brain shrinkage seen in human alcoholics, are cause for optimism, since they imply that abandonment of the alcoholic life-style may result in functional and in anatomic reconstitution of an essentially normal brain. The neuropathologic consequences of continued alcohol use beyond the duration used herein remain unknown. The fact that frank dementia does eventually occur in the heavy drinker suggests the presence of greater neuropathologic changes than those seen in our animal model.

References

1. Van Horn G. Dementia. *Am J Med.* 1987;83:101-110.
2. Carlen PL, Wortzman G, Holgate RC, Wilkinson DA, Rankin JG. Reversible cerebral atrophy in recently abstinent chronic alcoholics measured by computed tomography scans. *Science.* 1978;200:1076-1078.
3. Harper C, Kril J. Brain atrophy in chronic alcoholic patients: a quantitative pathological study. *J Neurol Neurosurg Psychiatry.* 1985;48: 211-217.
4. Harper CG, Kril J, Daly J. Are we drinking our neurones away? *BMJ.* 1987;294:534-536.
5. De la Monte SM. Disproportionate atrophy of cerebral white matter in chronic alcoholics. *Arch Neurol.* 1988;45:990-992.
6. Harper C, Krill J, Daly J. Does a moderate alcohol intake damage the brain? *J Neurol Neurosurg Psychiatry.* 1988;51:909-913.
7. Nutrient Requirements of Dogs. *A Report of the Committee on Animal Nutrition.* Washington, DC: National Academy of Sciences, National Research Council; 1962;8:989.
8. Adreanov OS, Mering TA. *Atlas of the Canine Brain.* Ann Arbor, Mich: Edward Brothers Inc; 1964.
9. Torvik A. Brain lesions in alcoholics: neuropathologic observations. *Acta Med Scand.* 1987; 717(suppl):47-54.
10. Lishman WA. Brain damage in alcoholism: current concepts. *Acta Med Scand.* 1987; 717(suppl):5-17.
11. Carlen PL, Wilkinson DA. Reversibility of alcohol-related brain damage: clinical and experimental observations. *Acta Med Scand.*1987; 717(suppl):19-26.
12. Harper CG, Kril JJ, Holloway RL. Brain shrinkage in chronic alcoholics: a pathological study. *BMJ.* 1985;290:501-504.
13. Lancaster FE, Philips SM, Patsalos PN, Wiggins RC. Brain myelination in the offspring of ethanol-treated rats: in utero versus lactational exposure by cross fostering offspring of control, pairfed, and ethanol treated dams. *Brain Res.* 1984;309:209-216.
14. Alling C, Bostrom K. Demyelination of mammillary bodies in alcoholism: a combined morphological and biochemical study. *Acta Neuropathol.* 1980;50:77-80.
15. Begleiter H, Porjesz B, Chou CL. Auditory brainstem potentials in chronic alcoholics. *Science.* 1981;211:1064-1066.

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Lower Extremity Motor Evoked Potentials in Multiple Sclerosis

Seth M. Jones, MD; Leopold J. Streletz, MD;
Vicki E. Raab, MD; Robert L. Knobler, MD, PhD; Fred D. Lublin, MD

• Transcranial magnetic stimulation was performed on 25 patients with definite multiple sclerosis. Motor evoked potentials were recorded from the anterior tibial muscle. Central motor conduction time was calculated using the equation $(F + M - 1)/2$ by stimulation of the common peroneal nerve. Motor evoked potentials were capable of detecting subclinical pyramidal tract lesions in multiple sclerosis. In patients with multiple sclerosis, the incidence of abnormality of motor and somatosensory evoked potentials was similar. Central motor conduction time was correlated with overall and pyramidal tract subscores on the Kurtzke Disability Status Scale and the Scripps Neurological Rating Scale. Central motor conduction time abnormalities correlated best with the presence of a Babinski's sign but also correlated significantly with weakness and hyperreflexia.

(*Arch Neurol.* 1991;48:944-948)

Magnetic coil (MC) stimulation of the human motor system has received increasing attention in the clinical neurophysiological literature since its introduction by Barker and coworkers[1] in 1985. The advantages of this technique over transcranial electrical stimulation are less patient discomfort, more consistent stimulation of deeper neural structures, and ease of stimulus application.[2] Minor disadvantages are the relative dispersion of the response wave forms, variability of the amplitude of these wave forms with successive stimulation, and the uncertainty of location of the precise point of MC stimulation.[3]

Electrical stimulation of the motor pathways has been used to study multiple sclerosis (MS) in both upper and lower extremities.[4-6] Magnetic coil stimulation techniques have been used to study motor evoked potentials (MEPs) in patients with a variety of neurologic disorders including MS.[7-12] Most of those studies using electrical stimulation focused primarily on the responses obtained from the upper extremities. These studies often included determinations of central motor conduction time (CMCT), but usually in combination with transcutaneous electrical stimulation of the spinal cord and motor roots.[2] Several studies have used MC stimulation to obtain MEPs and to calculate CMCT to the lower extremities.[8,10-12] The purpose of our study was to determine if MC stimulation and MEPs in the lower extremities were clinically useful in patients with definite MS. Our technique differed from that of other investigators in that the entire procedure was performed with the MC and utilized a method of CMCT determination involving M- and F-wave latencies. We examined correlations between MEP parameters and our patients' neurologic signs.

PATIENTS AND METHODS

Patients and Control Subjects

Control subjects consisted of 30 healthy volunteers (19 men and 11 women) with a mean age of 30.5 years (range, 19 to 50 years). The patient group was drawn from the Multiple Sclerosis Center of Thomas Jefferson University Hospital, Philadelphia, Pa, and consisted of 25 hospitalized patients with the diagnosis of definite MS.[13] There were 14 women and 11 men with a mean age of 40.8 years (range, 32 to 52 years).

All subjects gave informed consent to a protocol approved by the Thomas Jefferson University Hospital institutional review board. All patients had neurologic examinations with particular attention to pyramidal tract signs. Motor strength was assessed by the 0 to 5 Medical Research Council scale, and all patients were scored on the Kurtzke Expanded Disability Status Scale[14] and the Scripp's Neurological Rating Scale.[15] In addition to the MEP studies, all patients with MS had lower extremity somatosensory evoked potentials (SEPs) performed according to the American Electroencephalographic Society guidelines.[16] Most underwent magnetic resonance imaging of the brain and spinal cord and cerebrospinal fluid immunoglobulin studies.

MEP Stimulation and Recording Technique

Magnetic coil (Caldwell MES-10) stimulation was accomplished with a 9.5-cm circular coil that generated a 2.2-T sinusoidal pulse at 100% output. The common peroneal nerve was stimulated at the fibular head. The coil was held tangentially with the coil edge positioned over the nerve. The MEPs were recorded using standard electromyograph electrodes with the active lead over the motor point of the anterior tibial muscle and the reference lead over the anterior tibial tendon. The response was recorded with a conventional electromyograph (Teca TD-10) using a cathode ray tube with a sweep of 50 to 100 milliseconds [ms] and a sensitivity of 0.5 to 1.0 mV per division. Transcranial MC stimulation of the motor cortex was obtained with the coil held tangentially to the scalp, 15 cm rostral to the inion. The center was slightly posterolateral to the vertex. The MEPs were first recorded with the foot of the target limb slightly dorsiflexed (5% to 10% maximum contraction), which facilitated the response. This was followed by a second recording at rest. Stimulus intensity was set between 80% and 100% output. If there was any variation in the latency of anterior tibial muscle responses to transcranial, lumbar, or peripheral magnetic stimulation, the shor-

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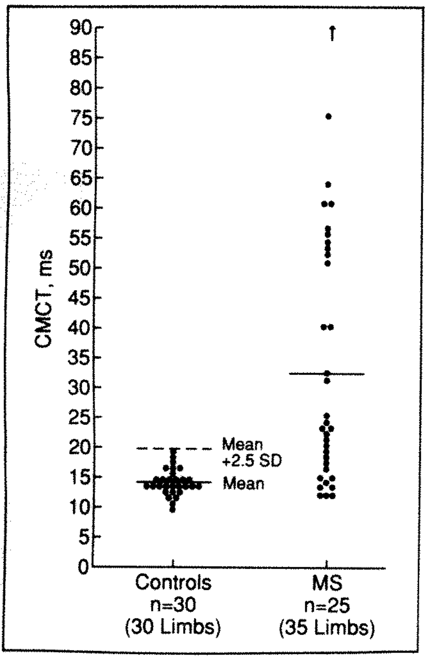

Fig 1.—Scattergram of central motor conduction time (CMCT) in the lower extremities of 30 control subjects (left) and 25 patients with multiple sclerosis (MS) (right). Recordings were made from one limb in the control group and from both limbs in patients with MS. Responses were obtained in 34 of 50 limbs in the latter group. Unobtainable responses were abnormal but are not reflected in the mean (solid line) or the standard deviation (dashed line). Some markedly prolonged values in the MS group are not included on the graph (arrow).

Table 1.—Comparison of Motor Evoked Potential (MEP) and Somatosensory Evoked Potential (SEP) in the Lower Extremities

	Total No.	Bilaterally Normal	Bilaterally Abnormal	Unilaterally Abnormal
MEP	25	4	18	3
SEP	25	5	20	0

test measured response was used for data analysis. In all subjects, peroneal nerve stimulation was necessary both to evaluate the integrity of the peripheral nerve and to measure peripheral latencies (M- and F-wave latencies) to the compound muscle action potential in the anterior tibial muscle. The M- and F-wave latencies and the MEP latencies were measured to the nearest 0.1 ms, and the baseline peak amplitude was measured to the nearest 0.1 mV.

The CMCTs were calculated using an indirect method of measuring peripheral contribution to the MEP latency using the formula (F+M-1)/2. This was subtracted from the MEP latency to yield the CMCT. This method for obtaining F-wave latencies with peripheral magnetic stimulation has been described elsewhere.[17-21] Magnetic stimulation was used instead of conventional electrical stimulation because no significant differences were found between the two methods in several normal subjects. Using the MC for both peripheral and cortical stimulation made the procedure less time-consuming to perform and more comfortable for the subjects.

If the F wave was atypical, the latency obtained with direct stimulation of the lumbar roots were used to measure peripheral conduction and to calculate the CMCT to confirm the reliability of the F-wave measurement. This was accomplished with the coil held tangentially at the midline over the L4-5 interspace. The latencies of the recorded responses to lumbar stimulation remained constant, with minor variations in coil position. Lumbar stimulation gave a consistently shorter measure of the peripheral component of the MEP latency than that obtained using F-wave latencies, resulting in a proportionately longer calculated CMCT. These findings were consistent with results from previous work in our laboratory and others.[17,22]

Data Analysis

The criteria for MEP abnormalities in the patient population consisted of the absence of an MEP response at rest or with dorsiflexion, prolongation of the MEP latency, or CMCT greater than 2.5 SD above the mean values derived from the control subjects. The MEP amplitude was not used as a criterion in the evaluation of the patients because of the large intertrial variability of this parameter in previous studies.[8] The SEP abnormalities were assessed using the amplitude and latency criteria established by the American Electroencephalographic Society.[16]

Statistical correlations between MEP and SEP findings and clinical neurologic signs were made using a χ^2 test. The Kurtzke scale subscores for pyramidal function (weakness) and spasticity, and the Scripps subscores for motor strength, deep tendon reflexes, and Babinski's sign, were correlated with CMCT using Spearman's rank correlation coefficients.

RESULTS

Magnetic coil stimulation was well tolerated by both control subjects and patients. No untoward side effects were encountered in patients or volunteers to MC stimulation of the head or limbs. None of the subjects with MS have developed seizures since being stimulated. Reproducible MEPs from the anterior tibial muscle were obtainable in all normal subjects in both the relaxed and facilitated states. Although some investigators report occasional absence of resting MEPs in the lower extremities with MC stimulation, we believe that this is attributable to differences in MC equipment and technique.[10] Other investigators using similar equipment and technique have had similar success.[21] The control group data yielded a mean MEP latency of 30.6 ms (range, 6.7 to 35.2 ms; SD ± 2.2 ms). The mean CMCT measured with F waves had a value of 13.8 ms (range, 9.7 to 18.0 ms; SD ± 1.9 ms). The mean CMCT measured with lumbar stimulation had a value of 16.2 ms (range, 12.6 to 19.3 ms; SD ± 1.7 ms). These measurements showed considerable reliability and stability.[17]

In seven of the 25 patients with MS who were studied, the MEP responses were not obtainable in either limb. In two patients, MEP responses could be obtained in only one limb. In the 18 patients with MS in whom MEPs were recorded, the mean MEP latency was 49.6 ms (SD ± 20.7 ms) at rest, and the mean CMCT was 33.7 ms (SD ± 22.5 ms). Some values were markedly prolonged (Fig 1). For each patient, the resting MEP response was used to calculate the CMCT. Thus, the MEP was abnormal in 21 of the patients with MS (84%) in either one limb (4/25) or both limbs (17/25). Four patients had normal MEPs in both legs. All patients had lower extremity SEPs performed, and these compared favorably ($\chi^2 = 27.1$; $P = .0001$) with the MEP results (Table). Of the 50 limbs evaluated, 34 (68%) demonstrated abnormalities in both MEP and SEP studies. In no patient in whom the MEP was bilaterally normal was a SEP abnormality found. In one limb of a patient with MS, the MEP was abnormal, while the SEP was normal. In four patients (16%), the MEPs and the SEPs were bilaterally normal. In no patients were peripheral motor or sensory conduction abnormalities detected using these methods.

In one patient in whom the diagnosis of MS had not been initially established, an MEP abnormality was detected in the right leg in the absence of weakness, hyperreflexia, or a Babinski's sign. The MEPs obtained from the arms were normal, but the lower extremity SEPs were abnormal and correlated with a sensory disturbance. Subsequently, the visual evoked potentials, cerebrospinal fluid IgG index, oligoclonal bands, and magnetic resonance imaging studies of the brain and spinal cord confirmed the diagnosis of MS (Fig 2). This patient illustrates how this technique may be capable of demonstrating subclinical motor dysfunction.

With regard to the correlation of MEP abnormalities and clinical signs, the MEP parameters of amplitude, latency, and CMCT were assessed. The variability of the amplitudes of the responses, even in normal subjects, made

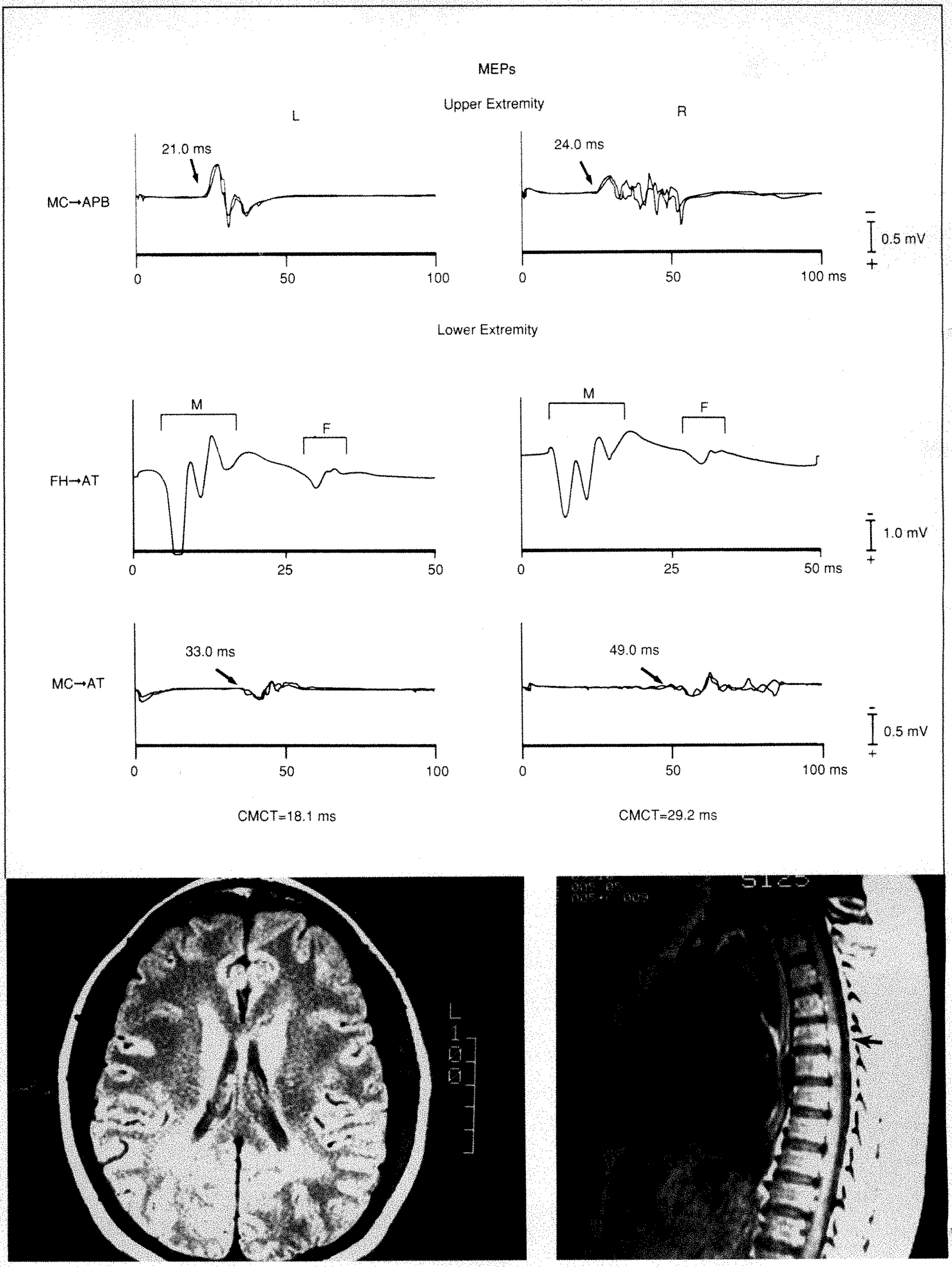
MEPs
Upper Extremity
L
R
21.0 ms
24.0 ms
MC→APB
0.5 mV
0
50
100
100 ms
Lower Extremity
M
F
FH→AT
1.0 mV
25
50 ms
33.0 ms
49.0 ms
MC→AT
CMCT=18.1 ms
CMCT=29.2 ms

Figure 2.

Fig 2.—A 34-year-old woman presented with paresthesias of hands and feet. Results of motor, cranial nerve, and cerebellar examinations were normal. Sensory examination revealed decreased vibration sense in the right and left feet. The deep tendon reflexes were brisk and symmetrical with flexor plantar responses. The cerebrospinal fluid had oligoclonal banding (IgG%, 23; IgG index, 1.0). Median nerve somatosensory evoked potentials were normal, but the right posttibial somatosenosory evoked potential showed a delayed P38 component. Top, Motor evoked potentials (MEPs) were performed on upper and lower extremities. Stimulation was applied at the motor cortex (MC) with recording at the abductor policis brevis (APB) and anterior tibial (AT) muscles. Upper extremity MEPs were normal. Lower extremity MEPs were normal on the left and delayed on the right (arrow) with a prolonged central motor conduction time (CMCT). The CMCT was calculated using M- and F-wave latencies obtained in recordings from stimulation at the fibular head (FH). Bottom left, Axial, first-echo, T_2-weighted magnetic resonance image of the brain shows multiple white matter lesions in the parietal and occipital regions with sparing of the cerebral motor pathways. Bottom right, An enhanced T_1-weighted sagittal magnetic resonance image of the thoracic spine demonstrated a high-signal lesion at the T-6 level of the spinal cord (arrow) consistent with an acute multiple sclerosis plaque.

it difficult to correlate amplitude with either CMCT or degree of disability. Others have found this same problem when looking at the lower extremity.[8] Using a χ^2 test, the presence or absence of an MEP abnormality correlated rather poorly with the classic pyramidal tract signs of motor weakness, spasticity, and hyperreflexia. However, with this statistical test, the CMCT slowing correlated significantly with the plantar response ($\chi^2 = 7.6$; $P = .01$).

To compare MEP data (CMCT) with nonparametric ordinal rating scales (Scripps and Kurtzke), we utilized the Spearman rank correlation coefficient. This was optimized by selecting the motor subscores for the lower extremities (Table 2). The Scripps scale yielded significant correlations when the CMCT was compared with motor weakness, deep tendon reflexes, and plantar response. No correlation was found with the Kurtzke subscores. The Kurtzke subscores for pyramidal signs (weakness) and spasticity do not allow for analysis of the legs alone or of the individual extremities. This probably accounts for much of the lack of correlation between these scores and the CMCT. Attempts at simple correlation between global neurologic deficits using either the total Scripps Neurological Rating Scale score or the Kurtzke Extended Disability Status Scale score did not reach statistical significance (Fig 3).

COMMENT

Our observation of a high incidence of MEP abnormalities in MS (84% of patients with definite MS) is similar to the results of lower extremity SEP studies.[23,24] Quantifying the incidence of abnormality is a necessary step in establishing the clinical accessibility of the involved central motor pathways to study using this new electrophysiological technique. The use of MC stimulation for both peripheral and central stimulation is an innovation that we have made in our technique. Although some controversy exists regarding the clinical applicability of MC stimulation of peripheral nerves in routine electromyographic studies,[25,26] in our laboratory no significant differences have been observed between magnetic and electrical stimulation of peripheral nerves for purposes of determining the latency of M or F waves. Also, the F-wave technique gives a consistently shorter and more accurate measurement of CMCT than does lumbar stimulation. This is because in lumbar stimulation the nerve roots are stimulated; therefore, conduction through the more proximal roots to the alpha motoneurons is not part of the measurement of peripheral conduction times.[17,20-22] Additionally, this technique afforded ease of recording and less patient discomfort than did conventional electrical stimulation.

Our incidence of MEP abnormalities is slightly higher than that found in previous MS studies in which the responses obtained in distal muscles of the upper extremities were examined. We believe that this may be attributable to several factors. The parasagittal location of the leg on the mesial frontal motor cortex makes it less accessible to MC stimulation. Additionally, the number of pyramidal tract fibers reaching the lumbosacral segments of the spinal cord is relatively small compared with the cervical region supplying arm muscles.[27,28] These anatomical facts may have resulted in a higher percentage of absent responses. However, the most likely reason for the increased percentage of abnormalities is that by recording from the lower extremity the efferent motor volley must traverse a longer pathway through the brain and spinal cord. Therefore, it is more likely to encounter a demyelinated region, resulting in an abnormal MEP. Small demyelinating lesions in the pyramidal tract have been suspected to be a frequent early clinical sign of MS.[29,30]

Table 2.—Correlation of Neurologic Scales and Central Motor Conduction Time*

Pyramidal Tract Signs	Scripps Score	Kurtzke Score
Motor weakness	$P = .05$	NS
Spasticity	. . .	NS
Deep tendon reflexes	$P = .05$	. . .
Plantar response	$P = .05$	. . .

*NS indicates not significant.

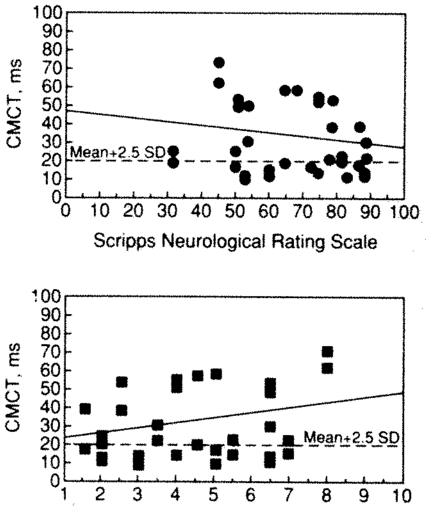

Fig 3.—Linear regression graphs comparing values for central motor conduction times (CMCTs) with the overall scores for the Scripps (upper graph) and Kurtzke scales (lower graph) for rating the neurologic examination in patients with multiple sclerosis. Note that a lower Scripps score and a higher Kurtzke score indicate greater disability. Some normal CMCT values were found in patients with Scripps and Kurtzke scores reflecting severe disability. This happened in cases in which the disability was caused by nonpyramidal lesions. The regression lines show a definite trend; however, these did not reach statistical significance. The dashed line shows the upper range of normal (mean + 2.5 SD) for CMCT from the control data.

The typical MEP abnormalities that we found were the same as those found by others who studied the upper extremities, ie, prolongation of latency or an absent response.[3,6-12] The delay in the CMCT measurements of our patients with MS is entirely consistent with the type and degree of electrophysiological abnormality in MS, ie, central demyelination. This probably arises as a result of conduction block of the corticospinal fibers, selective fiber loss in this pathway with utilization of other multisynaptic motor pathways, or the failure of high-frequency conduction responsible for the temporal summation of excitory postsynaptic potentials at the level of the lumbar spinal motoneuron.[31] The abnormalities of the MEP in the lower extremities of patients is not specific to MS or to demyelinating disease. In our laboratory and others, similar abnormalities have been revealed by MEPs in patients with cerebral and spinal cord dysfunction of other cause, including stroke, trauma, and degenerative disorders.[6,10,32,33]

The correlations between the clinical signs and neurologic rating scales need clarification. Like other evoked potential studies, MEPs are capable of demonstrating subclinical lesions of the brain and spinal cord. The presence of MEP-detected but clinically silent lesions and severe disability secondary to nonpyramidal tract lesions, ie, coordination, vision, and bowel or bladder involvement, reduced correlation between the CMCT and the overall Scripps and Kurtzke scores. This latter problem was eliminated by using the Scripps and Kurtzke subscores for signs reflecting only the involvement of the pyramidal tract. The Scripps scale showed certain advantages over the Kurtzke scale in that individual lower extremity ratings could be subscored to yield better correlation. It is notable that among the classic pyramidal tract signs, the Babinski sign correlated best with MEP abnormalities. Nevertheless, motor weakness and hyperreflexia correlated with CMCT when the individual lower extremities were considered separately. These observations suggest that quantitative assessment of motor deficits may be obtained in patients with MS. This may overcome some of the shortcomings of the more global neurologic rating scales and measurements of motor strength.[34] Measurements obtained in transcranial MC stimulations and MEPs may provide data that are more amenable to statistical analysis with which to determine clinical changes in the course of disease or following therapy.[35,36]

In summary, MEP abnormalities may be found with a high incidence in patients with definite MS. These abnormalities include absence and delays of the MEP and prolongation of the CMCT. These may occur in the absence of clinical signs of motor dysfunction. The MEP abnormalities correlated with the SEP abnormalities in the legs. The CMCT abnormalities clinically correlated best with pyramidal tract signs. Global neurologic rating scales also show a trend toward correlating with MEP abnormality in the more neurologically disabled patients with MS. Thus, MEPs in the lower extremity appear to be a valuable procedure in the diagnosis and evaluation of motor deficits in patients with MS. Studies of patients with MS who lack clinical signs of motor involvement will determine whether MEPs in the lower extremities will be as useful as other evoked potentials in detecting subclinical effects of demyelination in the central nervous system.

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References

1. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of motor cortex. *Lancet.* 1985;2:1106-1107.

2. Merton PA, Morton HB. Stimulation of the cerebral cortex in the intact human subject. *Nature.* 1980;285:227.

3. Barker AT, Freeston IL, Jarratt JA, Jalinous R. Magnetic stimulation of the human nervous system: introduction and basic principles. In: Chokroverty S, ed. *Magnetic Stimulation in Clinical Neurophysiology.* Stoneham, Mass: Butterworths; 1990:55-70.

4. Cowan JMA, Dick JPR, Day BL, Rothwell FC, Thompson PD, Marsden CD. Abnormalities in central motor pathway conduction in multiple sclerosis. *Lancet.* 1984;2:304-307.

5. Mills KR, Murray NMF. Corticospinal tract conduction times in multiple sclerosis. *Ann Neurol.* 1984;18:601-605.

6. Berardelli A, Inghiller M, Prior A, Accornero N, Manfredi M. Electrical stimulation of motor cortex in patients with motor disturbances. In: Rossini PM, Marsden CE, eds. *Non-invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications.* New York, NY: Alan R Liss Inc; 1988:219-230.

7. Hess CW, Mill KR, Murray NMF. Measurement of central motor conduction times in multiple sclerosis by magnetic stimulation. *Lancet.* 1986;2:355-358.

8. Ingram DA, Thompson AJ, Swash MJ. Central motor conduction in multiple sclerosis: evaluation of abnormalities revealed by transcutaneous magnetic stimulation of the brain. *J Neurol Neurosurg Psychiatry.* 1988;51:487-494.

9. Caramia MD, Zarola F, Spadaro M, Pardal AM, Bernardi G. Neurophysiological testing of the central impulse propagation characteristics in patients with sensorimotor disorders. In: Rossini PM, Marsden CD, eds. *Non-invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications.* New York, NY: Alan R Liss Inc; 1988:207-218.

10. Eisen A, Shtybel W. Clinical experience with transcranial magnetic stimulation. *Muscle Nerve.* 1990;13:995-1011.

11. Ingram DA. Central motor conduction in neurologic disorders: studies with electrical and magnetic brain stimulation. In: Rossini PM, Marsden CD, eds. *Non-invasive Stimulation of Brain and Spinal Cord: Fundamentals and Clinical Applications.* New York, NY: Alan R Liss Inc; 1988:207-218.

12. Jarratt JA, Barker AT, Freeston IL, Jalinous R, Kandler RH, Jaskolski D. Magnetic stimulation of the human nervous system: clinical applications. In: Chokroverty S, ed. *Magnetic Stimulation in Clinical Neurophysiology.* Stoneham, Mass: Butterworths; 1990:185-203.

13. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol.* 1983;113:227-231.

14. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (DSS). *Neurology.* 1983;33:1444-1452.

15. Sipe JC, Knobler RL, Braheny SL, Rice GPA, Panitch HS, Oldstone MSA. A neurologic rating scale (NRS) for use in multiple sclerosis. *Neurology.* 1984;34:1368-1372.

16. American Electroencephalographic Society. Guidelines for clinical evoked potential studies. *J Clin Neurophysiol.* 1984;1:3-53.

17. Booth KR, Streletz LJ, Raab VE, Kerrigan JJ, Alaimo MA, Herbison GJ. Motor evoked potentials and central motor conduction: studies of transcranial magnetic stimulation to the leg. *Electroencephalogr Clin Neurophysiol.* 1991;81:57-62.

18. Rossini PM, Caramio MD. Methodological and physiological considerations on the electric or magnetic transcranial stimulation. In: Rossini PM, Marsden CD, eds. *Non-invasive Stimulation of the Brain and Spinal Cord: Fundamentals and Clinical Applications.* New York, NY: Alan R Liss Inc; 1988:37-65.

19. Hallett M, Cohen LG. Magnetism: a new method for stimulation of nerve and brain. *JAMA.* 1989;262:538-541.

20. Robinson LR, Puangpeth J, Maclean IC. Central motor conduction times using transcranial stimulation and F-wave latencies. *Muscle Nerve.* 1988;11:174-180.

21. Claus D. Central motor conduction: method and normal results. *Muscle Nerve.* 1990;13:1125-1132.

22. Ugawa Y, Rothwell JC, Day BL, et al. Magnetic stimulation over spinal enlargements. *J Neurol Neurosurg Psychiatry.* 1989;52:1025-1032.

23. Brooks EG, Wilson SL, Lentz KE, Chiappa KH, Young RN. A comparison of upper and lower limb SEP's in multiple sclerosis. In: Pederson E, Clausen J, Oadez L, eds. *Actual Problems in Multiple Sclerosis Research.* Copenhagen, Denmark: FADLs Forlag; 1983:38-44.

24. Bartel DR, Markand ON, Kolan J. The diagnosis and classification of multiple sclerosis: evoked responses and spinal fluid electrophoresis. *Neurology.* 1980;33:611-617.

25. Maccabee PT, Amassian VE, Cracco RQ, Cracco JA. An analysis of peripheral motor nerve stimulation in humans using the magnetic coil. *Electroencephalogr Clin Neurophysiol.* 1988; 70:524-533.

26. Evans BA, Litchy WJ, Daube JR. The utility of magnetic stimulation for routine peripheral conduction studies. *Muscle Nerve.* 1988;11:1074-1078.

27. Weil A, Lassek A. The quantitative distribution of the pyramidal tract in man. *Arch Neurol Psychiatry.* 1929;22:495-510.

28. Davidoff RA. The pyramidal tract. *Neurology.* 1990;40:333-339.

29. Kurtzke JF. Patterns of neurologic involvement in MS. *Neurology.* 1989;39:1235-1238.

30. Shibasaka H, McDonald WI, Kuroiwa Y. Racial modification of clinical picture of multiple sclerosis: comparison between British and Japanese patients. *J Neurol Sci.* 1981;49:253-271.

31. McDonald WI. Pathophysiology of multiple sclerosis. *Brain.* 1974;97:1235-1238.

32. Mills KR, Murray NMF. Magnetic and electrical transcranial brain stimulation: physiological mechanisms and clinical applications. *Neurosurgery.* 1987;20:164-168.

33. Bridges SL. Magnetic cortical stimulation in stroke patients with hemiparesis. In: Chokroverty S, ed. *Magnetic Stimulation in Clinical Neurophysiology.* Stoneham, Mass: Butterworths; 1990: 233-247.

34. Visser SL, Aaren A. Evaluation of EMG parameters for analysis and quantification of hemiparesis. *Electromyogr Clin Neurophysiol.* 1981; 21:591-610.

35. Katz S, Ford AB, Moskowitz RW, et al. Studies of illness in the aged: index of ADL: a standardized measure of biological and psychological function. *JAMA.* 1963;185:914-919.

36. Kurtzke JF. Neuroepidemiology, II: assessment of therapeutic trials. *Ann Neurol.* 1986; 19:311-319.

Frontal Verbal Amnesia

Phonological Amnesia

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• Although aphasic patients with frontal lobe damage may demonstrate impaired retention of verbal material, significant anterograde memory disturbances have not, to our knowledge, been reported with a minor Broca's aphasia. We describe a patient with minor Broca's aphasia who exhibited an unusual and profound anterograde memory disturbance, especially for phonologically specified stimuli. We suggest that this disturbance is attributable to an impairment in the volitional, controlled search of stored phonological information.

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A number of investigators have demonstrated that anterior aphasia may be associated with impaired retention of verbal material.[1-3] Cermak and Moreines,[4] for example, reported that patients with nonfluent aphasia were impaired on a phonological memory task involving the detection of rhymes; they proposed that anterior aphasia induced a defect of "phonemic recirculation." More recently, Cermak and coworkers[5] have further suggested that the memory deficits of anterior aphasics may be related to an inability to compare phonological items already in memory and difficulty in "reconstructing" items based on phonological features.

Broca's aphasia is typically associated with lesions involving Broca's area as well as portions of the anterior perisylvian region, including the sensory motor cortex, insula, and anterior parietal operculum.[6] Smaller lesions largely or entirely restricted to Broca's area, however, have also been shown to be associated with a language disturbance; this syndrome, designated *minor Broca's aphasia* by Foix,[7] is characterized by a combination of difficulties, often including word-finding disturbance, effortful articulation, and decreased verbal fluency. Although sometimes initially severe, these symptoms are typically transient, and persistent, overt language disturbances are uncommon.

Although nonaphasic patients with left frontal lobe lesions may have lexical retrieval impairments, as evidenced by their poor performance on controlled word association tasks,[8,9] to our knowledge significant anterograde memory disturbances have not been reported with a minor Broca's aphasia. We describe a patient with minor Broca's aphasia subsequent to an ischemic infarction involving Broca's area and small portions of the inferior and middle frontal gyri who exhibited an unusual and profound anterograde memory disturbance; we suggest that this disturbance is attributable to an impairment in the volitional, controlled search of stored phonological information.

REPORT OF A CASE

The patient was a right-handed 59-year-old man who was admitted for evaluation of a memory impairment. He had been in excellent health until 3 years prior to admission when, 1 week after a transient episode of left-eye blindness, he noted the sudden onset of difficulty in speaking and weakness of the right side of his body. Neurologic evaluation at that time revealed a mild right hemiparesis, a nonfluent aphasia with mildly impaired auditory comprehension, and a Gerstmann's syndrome. The auditory comprehension impairment and Gerstmann's syndrome resolved within several days. Unfortunately, no additional information about the patient's initial language impairment is available.

Although family members noted no impairment in his speech after the stroke, the patient considered himself to be appreciably less articulate because he had difficulty in finding the appropriate word and in "getting words out."

In the estimation of the patient and his family, however, his subtle speech impairment paled in significance relative to the severe and disabling memory deficit noted subsequent to his stroke. Although he believed his memory for faces, pictures, and places to be relatively unimpaired, he stated that his memory for names and verbal material, whether written or spoken, was quite poor. As a consequence of his memory deficit, he was unable to return to his job as a loan officer for a finance company; he worked briefly as a prison officer before his memory disturbance forced him to retire.

Neurologic examination 3 years after the stroke revealed a mild spastic weakness and clumsiness of the right hand. Evaluation of the patient's higher nervous system functions revealed that his spontaneous speech, although marked by occasional word-finding pauses, was fluent, with normal prosody and articulation. His discourse contained a normal range of syntactic structures. Naming, although occasionally hesitant, was normal. Repetition of words, phrases, and sentences was excellent; sentences of up to 12 words, as well as sentences with unusual syntactic structures, such as center-embedded clauses, were repeated perfectly. Auditory comprehension was unimpaired. The patient read aloud and for comprehension quite well. No effect of orthographic regularity, part of speech, or imagery was noted in his reading. His writing was normal. Calculations, right-left discrimination, and finger naming were normal. No buccofacial or limb apraxia was noted. There was no neglect. He was able to draw a cube, as well as maps of the United States.

A computed tomographic scan performed 3 years after the patient's stroke revealed an old area of infarction involving Broca's areas, as well as more rostral portions of the inferior frontal gyrus. Additionally, small portions of the precentral and middle frontal gyri were also infarcted (Figs 1 and 2).

NEUROPSYCHOLOGICAL EVALUATION

Intellectual

On the Weschler Adult Intelligence Scale, the patient obtained a verbal intelligence quotient (IQ) of 93, a performance IQ of 88, and a full-scale IQ of 91. His performance IQ was thought to have been adversely influenced by his right-hand clumsiness. The Peabody Picture Vocabulary Test[10] yielded a verbal IQ estimate of 103.

Language

A number of formal tests were administered for more careful assessment of the patient's language capacities. His performance on the Western Aphasia Battery[11] and selected portions of the Boston Diagnostic Aphasia Examination,[12] including the reading, repetition, and writing subtests, was essentially perfect. For further assessment of the patient's auditory comprehension, the Token Test[13] was administered; the patient made one mistake on subtest VI, but otherwise his performance was perfect. He performed normally on the Boston Naming Test[14]; the Florida Syntax Comprehension Test,[15] in which correct performance is critically dependent on comprehesion of the distinction between indirect and direct objects; and the Battery of Adult Reading Function,[16] a test that assesses reading comprehension and the reading aloud of reg-

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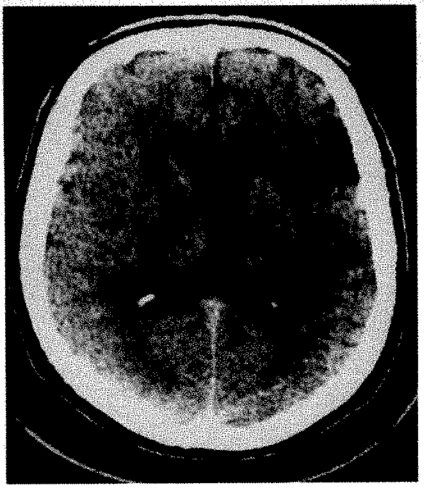


Fig 1.—A low ventricular computed tomographic scan image demonstrating an infarct involving the inferior frontal gyrus.

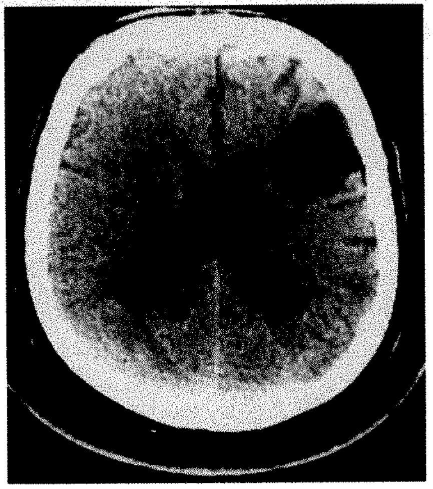


Fig 2.—A high ventricular computed tomographic scan image demonstrating an infarct involving the inferior frontal gyrus and small portions of the middle frontal gyrus.

ular and irregular nouns, functors, and nonwords. The Story Completion Test[17] was also administered; with a single exception, the patient generated a response of the desired syntactic form.

Frontal Lobe Tasks

Several cognitive tasks sensitive to frontal lobe functioning were administered. The patient performed poorly on the Wisconsin Card Sorting Test[18]; he failed to detect the correct sorting principle after 35 trials. Approximately 20% of his errors were random guesses and 50% were perseverative errors. The patient was also impaired on the color-naming and interference subtests of the Stroop Interference Task.[19] He required 88 seconds to name color patches (1.5 SDs below the mean) and 288 seconds to complete the interference task (2 SDs below the mean). The patient demonstrated no perseveration in Luria's "mn" writing task but performed quite poorly on the "go–no go" and contrasting motor programs task.[20]

Attention and Memory

Digit span was assessed on a number of occasions. The patient correctly repeated 100% of orally presented five-digit lists and 60% of six-digit strings. Seventy-one percent of the errors were sequencing errors, and 29% of the errors were due to the omission of a single item. With visual presentation of single-digit written numbers at the rate of approximately one number per second, the patient's performance was quite similar. Administration of the Wechsler Memory Scale[21] revealed the patient to have a memory quotient of 71 (Table 1). His story recall of the logical memory stories from the Wechsler Memory Scale was six initially (average normal, 10) and four after a 20-minute delay (average normal, eight). His paired-associate learning was similarly impaired on word-list learning tasks, both with auditory and visual presentation. On the Rey Auditory Verbal Learning Test,[22] for example, he recalled no more than six of the 15 words across any of five learning trials, and his delayed 20-minute recall was three. Similar results were obtained with visual presentation. His memory performance fell more than 2 SDs below the mean of age-matched controls.

The patient's performance on the Rey Auditory Verbal Learning Test also provided an opportunity for assessment of the effects of recency and primacy in supraspan list learning. On the first five trials on both the auditory and visual versions of the Rey Auditory Verbal Learning Test, the patient correctly produced 90% of the 20 items presented in the last two positions. Additionally, the effects of recency and primacy were evaluated by calculation of the percentage of words reported as a function of position in the list; in the first five trials on the auditory and visual versions of the test, the patient correctly reported 20% of the words from the first third, 16% of the words from the middle third, and 72% of the words from the last third of the list. Thus, the patient exhibited a clear effect of recency but no clear effect of primacy.

In contrast, the patient performed much better on nonverbal recent memory tasks such as the Milner Facial Recognition Test[23] and Kimura's Recurring Figures Test.[24] He correctly identified nine of the 12 target faces and obtained a score of 44 on the latter task; his performance was in the normal range on both tasks.

Table 1.—Wechsler Memory Scale (Form I)

Information	6
Orientation	5
Mental control	6
Memory passages	6, 4 delayed
Digits total	8
Visual reproduction	5
Associate learning	1.5
Memory quotient	71

Thus, the patient performed normally on a wide range of language tasks and exhibited a normal verbal IQ. In spite of his at least relatively normal language skills, however, he has a marked verbal memory deficit with sparing of nonverbal memory. The following investigations were performed to further characterize the patient's memory impairment.

Rate of Forgetting.—As performance on tests assessing the rate of forgetting has been demonstrated to distinguish between amnestic syndromes caused by bitemporal vs diencephalic damage,[25-27] the patient's rate of forgetting was assessed in a manner similar to that described by Huppert and Piercy.[25] One hundred target stimuli (pictures) were individually projected on a screen for a period of 8 seconds each. At intervals of 10 minutes, 20 minutes, 90 minutes, 24 hours, and 1 week after this presentation, different random subsets of 20 pictures from the original sample and 20 new pictures were projected, and the patient was asked to indicate whether each picture was from the original list of stimuli. Five age- and education-matched controls were tested in a similar fashion, except that stimuli were presented for 1 second each. Although the difference in exposure times renders a comparison with control subjects difficult, it is apparent from examination of Fig 3 that the patient's performance was quite similar to that of five age- and education-matched controls, falling within 1 SD of their performance at every test interval.

The patient's rate of forgetting for verbal stimuli was also assessed in the manner described above. Stimuli for this experiment included 100 slides depicting a single typed word. The target words were presented for 8 seconds each, and the patient's recognition was assessed in the manner described above. The patient correctly sorted only 57% of the stimuli at both 10 and 20 minutes; as his performance was not above the chance level ($\chi^2 = 1.63$; $P > .1$), this investigation was discontinued after the second session. Errors included an almost equal number of false-positives and false-negatives. With a 1-second stimulus exposure, controls correctly identified 81% and 75% of stimuli at 10 and 20 minutes, respectively, and remained well above chance (67% correct) after 1 week (Fig 4).

Thus, the patient's rate of forgetting was essentially normal for "nonverbal" material; his rate of forgetting for verbal material could not be assessed, as we could not demonstrate evidence of adequate initial performance.

Effect of Interference.—A Peterson and Peterson[28] task adapted from Butters and Grady[29] was given to assess the effects of interference on the patient's verbal memory performance. On each trial, three semantically and phonologically unrelated monosyllabic or bisyllabic words were auditorally presented to the patient at the rate of approximately one word per second. Five trials were presented in each of four conditions: (1) immediate recall, in which there was no delay between stimulus presentation and production; (2) a 20-second unfilled delay between stimulus presentation and production, during which the patient was permitted to rehearse; (3) a 20-second filled delay, during which the patient was asked to count backward by twos before recalling the stimuli; and (4) a 4-second unfilled interval, during which the patient was encouraged to rehearse, followed by a 16-second period, during which the patient was asked to count backward by twos. In the immediate recall and 20-second unfilled delay conditions, the patient correctly produced all 15 of the target words; with a 20-second filled delay, the patient produced only two (13%) of 15 words; with a 4-second predistractor delay, followed by a 16-second filled delay, he produced nine (60%) of 15 words (Fig 5). On the latter two conditions, errors included 16 omissions and two intrusions. No semantic errors were noted. The patient's performance was quite similar with visual presentation of the stimuli. He made no errors in the immediate recall and unfilled delay conditions, and he correctly produced six (40%) of 15 stimuli with a 20-second filled delay and produced eight (53%) of 15 stimuli with a 4-second predistractor period and a 16-second delay and distraction. Errors included three intrusions and 13 omissions.

These data suggest that the patient is quite sensitive to the effects of interference or, alternatively expressed, dependent on continued rehearsal. In conjunction with the demonstration that the patient exhibited a relatively normal recency effect, these data suggest that rehearsal within the articulatory

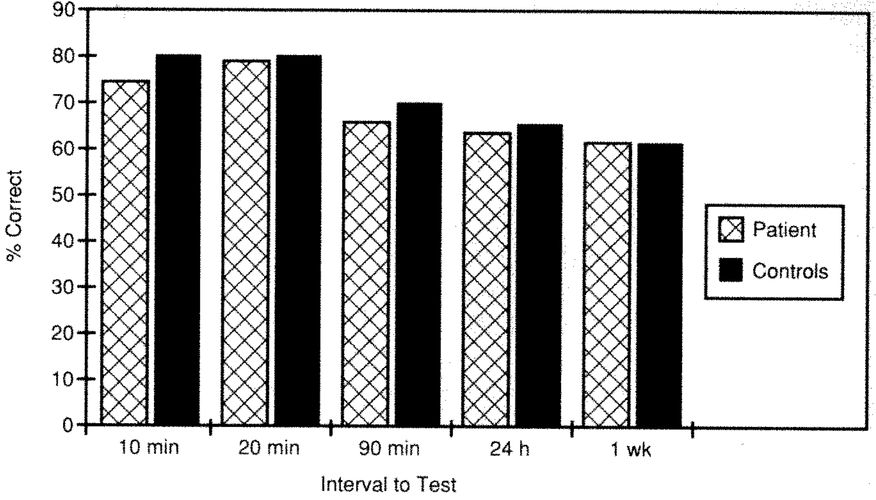


Fig 3.—Performance of the patient and controls, expressed as percentage correct, on a test assessing the rate of forgetting of pictures.

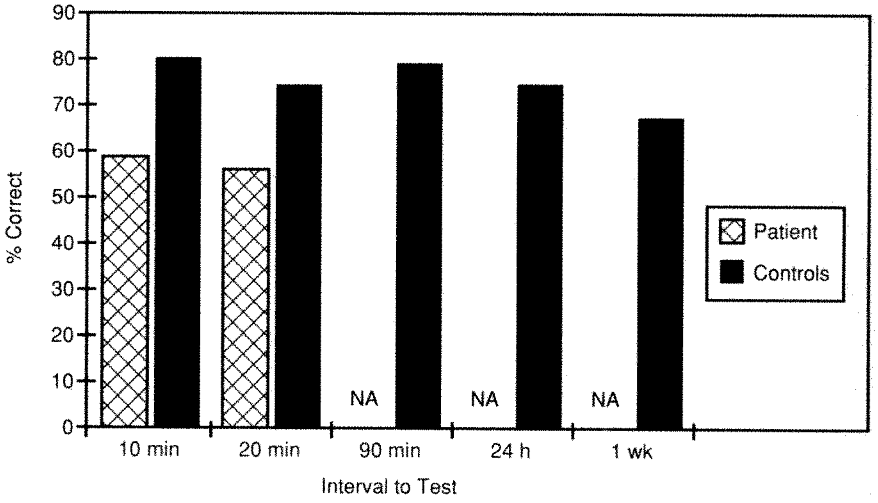
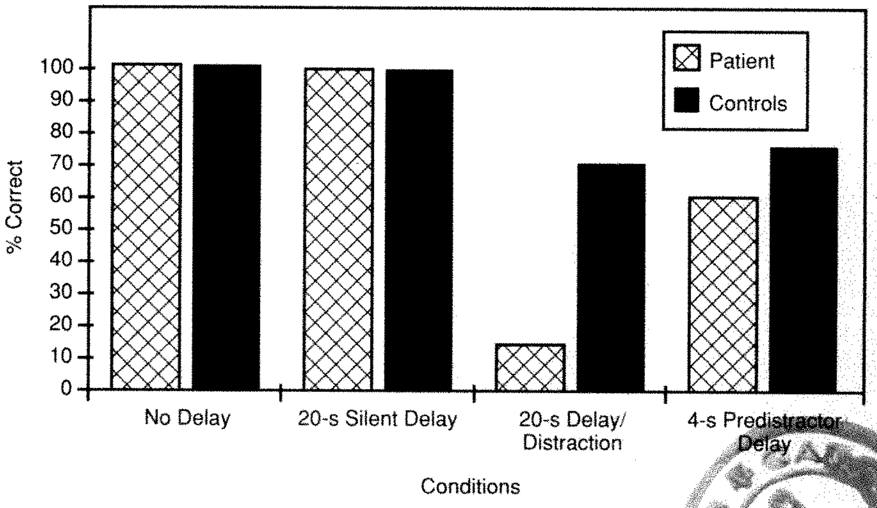


Fig 4.—Similar to Fig 3 except that stimuli were words rather than pictures. NA indicates not applicable.

Fig 5.—Percentage correct on a Peterson-Peterson memory task with auditory stimuli.



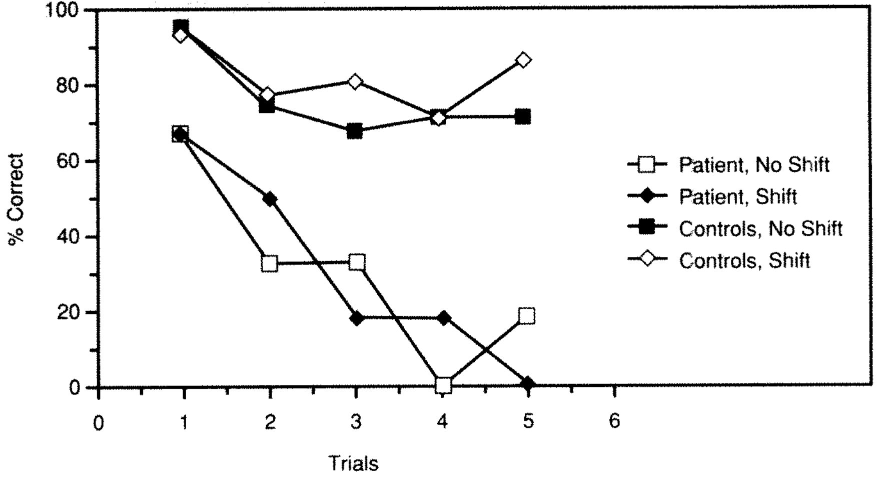


Fig 6.—The performance of the patient and controls, expressed as percentage correct, on a release from proactive inhibition task.

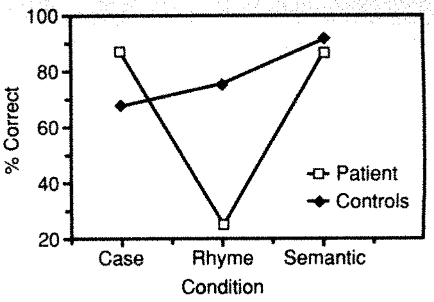


Fig 7.—Performance, expressed as percentage correct, of the patient and controls on a level of processing task with written stimuli.

loop is not impaired.

Release from Proactive Inhibition.—In an attempt to assess the possible role of impaired semantic/conceptual encoding in the production of the patient's memory deficit, a release-from-proactive-inhibition task similar to that of Cermak et al[3] was administered. This task was derived from Wickens'[30] modification of the Peterson and Peterson[28] distraction technique, in which subjects were given several consecutive trials of word stimuli, all of which belonged to the same semantic category (eg, fruits). This was followed by a trial in which the word stimuli were exemplars of a different category (eg, vegetables). As previously documented, memory performance in normal subjects deteriorates over trials, because of the buildup of proactive interference. Wickens[30] demonstrated, however, a dramatic improvement in memory performance on trials when the stimuli came from a different semantic category. This improvement presumably stemmed from a release of proactive interference that occurred because subjects had noted the change or shift in the semantic category of the stimulus words. The underlying assumption is that stimuli must be semantically encoded for the release effect to occur.

To assess release from proactive interference, the patient and controls were tested on a Peterson and Peterson[28] distraction task involving eight blocks of five trials. Stimuli for each trial consisted of three semantically related concrete nouns (eg, pear, apple, and grape) read aloud to the patient. After a 20-second delay filled with counting backward by twos, the patient was asked to produce the three target words. There were two conditions. In the *no-shift condition*, all five trials of the block consisted of word stimuli from the same semantic category (eg, fruit). In the *category shift condition*, word stimuli on trial 5 were from a different semantic category (eg, vegetables) than the preceding four trials of the block. Category shift and no-shift conditions were randomized, with 5-minute rest intervals between each block. The performance of the patient and normal controls across trials 1 through 5 of the categoryshift and no-shift conditions is shown in Fig 6. For both the patient and the controls, there was a progressive decline in performance across trials 1 through 4 of both conditions, with the patient exhibiting a greater decrement, which presumably reflects a greater susceptibility to interference. The patient, like amnesic patients with Korsakoff's psychosis,[3] exhibited no "release" effect. For controls, in contrast, the change in semantic class on trial 5 of the category shift condition was associated with a significant increase in recall as compared with the no-shift condition ($\chi^2=4.91$; $df=1$; $P<.05$).

The interpretation of this finding, however, is unclear. Some investigators[3] have argued that the finding indicates that the patients were not encoding in semantic categories. Alternatively, on the basis of a comparison of the performance of patients with frontal or temporal lobectomy on a release-from-proactive-inhibition task, Moscovitch[31] has argued that the phenomenon is more appropriately associated with frontal impairment than with memory loss.[32] Because our patient was impaired on tests of frontal lobe function as well as memory, the explanation for his failure to manifest the release phenomenon is not clear.

Memory for Phonology.—Levels of Processing.—Perhaps the most striking aspect of the patient's verbal memory deficit was a marked discrepancy between performance on tasks requiring registration and/or retrieval of phonologically, compared with semantically, specified items. This phenomenon was first noted on a task employing the "levels of processing" paradigm.[33] This experiment was motivated by a conceptual framework suggesting that the adequacy of memory registration is a function of the depth of analysis or the degree to which the stimulus is semantically processed.

Stimuli for this task included 36 target words printed on a 4 × 6-in card; half of the words were printed in uppercase and half in lowercase letters. Stimuli were shown to the patient for approximately 5 seconds each; immediately after the presentation of each stimulus, the patient was asked one of three types of orienting questions: (1) one third of the stimuli were accompanied by orthographic orienting questions (eg, "Is this word written in uppercase letters?"); (2) one third were accompanied by phonological orienting questions (eg, "Does this word rhyme with fear?"); and (3) one third were accompanied by semantic orienting questions (eg, "Is this a type of fruit?"). Ten minutes later, a recognition memory task was administered in which thirty-six 4 × 6-in cards, each containing one of the stimuli and three phonologically and semantically unrelated foils, were presented. The patient was asked to indicate which of the four words had been previously presented.

As depicted in Fig 7, the patient correctly identified 87% of the words introduced with a semantic orienting question, 87% of the words introduced with an orthographic orienting question, but only 25% of the words introduced with a phonological orienting question. In contrast, five age- and education-matched controls showed the expected pattern, correctly identifying 91% of the semantically, 75% of the phonologically, and 67% of the orthographically cued words.

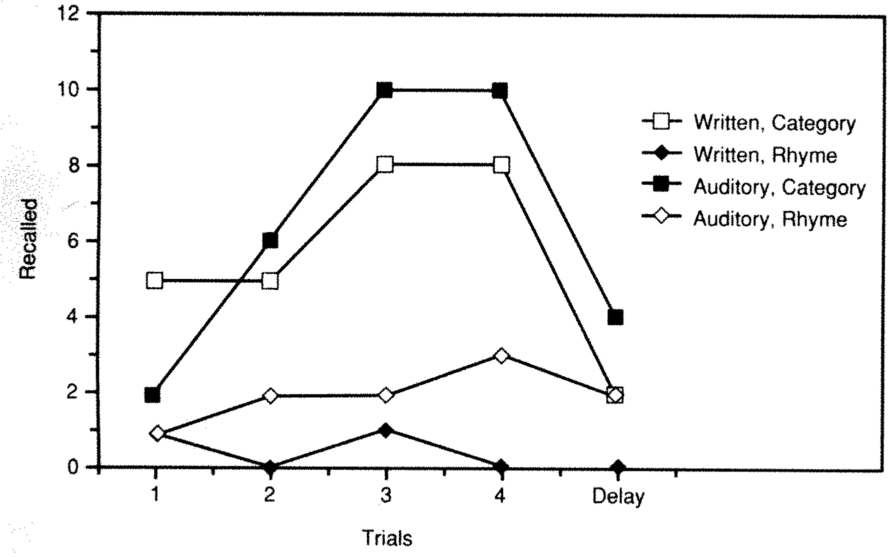


Fig 8.—Number of rhyming and semantically related paired associates recalled by the patient with auditory and written stimuli.

Table 2.—Fluency Tasks

	Patient	Controls
Letters		
f	2.4	. . .
a	2.0	. . .
s	2.6	. . .
Semantic categories	12.3	14.5
Rhyming words	2.0	8.4
Nonverbal (figures)	16.0	. . .

The patient's selective memory deficit for phonologically cued stimuli could not be attributed to an inability to make rhyme judgments, in that he was 100% accurate when answering rhyme orienting questions.

An auditory version of the levels of processing task was also performed. On this task, the orthographic orienting question was eliminated, and the patient was asked to indicate if the words were spoken in a male or female voice. The patient correctly identified 93% of the words presented with a semantic orienting question, 75% of the words introduced with a male/female voice orienting question, but only 25% of the words introduced with a phonological orienting question. Controls correctly identified 91%, 75%, and 67% of stimuli introduced with semantic, phonological, and voice orienting questions.

Rhyming Paired-Associate Tasks.—The patient's apparent deficit in memory for phonologically encoded and/or retrieved information was also assessed using two list-learning tasks adapted from Warrington and Weiskranz.[34] Stimuli for one task included 12 pairs of semantically related words (eg, "ask" and "inquire"); stimuli for the second task included 12 pairs of rhyming words (eg, "chair" and "bear"). The word pairs from each list were read to the patient at the rate of one word per second. After presentation of the paired-associate list, the patient was given the first word of the pair and asked to produce its associate. This procedure was repeated for a total of four trials for each of the two lists. Delayed recall of the word pairs was tested after a 30-minute delay. The semantically and phonologically related word pairs were presented in different sessions. Both visual and auditory versions of these lists were given.

The patient's performance with written and auditory stimuli presentation is presented in Fig 8. He performed better with semantically related stimuli on each trial with both written and auditory stimuli. With written stimuli, this difference reached significance on trials 2, 3, and 4 ($\chi^2=6.3$, 8.7, 12.0, respectively; all $P<.01$). With auditory stimuli, he performed significantly better with semantically related pairs on trials 3 and 4 ($\chi^2=10.7$and 8.2, respectively; both $P<.05$). Summing across the five trials, the patient performed significantly better with semantic, as compared with rhyming, paired associates with both written ($\chi^2=30.0$; $P<.01$) and auditory ($\chi^2=17.7$; $P<.01$) stimuli. Age- and education-matched controls demonstrated no significant difference between rhyming and semantically associated words on individual trials but did demonstrate a slight but consistent superiority with semantic paired associates which, summing over all five trials, was significant ($\chi^2=5.6$; $P<.05$).

Fluency Tasks.—The effect of phonological factors on retrieval of information from remote or long-term memory was assessed by a number of variants of the Thurstone Word Fluency Test[35] (Table 2). In one investigation, the patient's ability to generate words beginning with a designated letter was compared with his ability to generate words defined on the basis of semantic attributes. In the former task, the patient was instructed to generate in 1 minute as many words as possible that begin with the letter *f*; similar 1-minute trials were performed in which he was asked to generate words beginning with *a* and *s*. Data were collected for each of the three letters during five separate sessions. The patient was also instructed to generate in 1 minute as many exemplars as possible of a specified semantic category. Eight semantic categories were tested on each of two occasions.

As indicated in Table 2, the patient's average score for the letters *f*, *a*, and *s* was 2.4, 2.0, and 2.6 words per minute, respectively; thus, his average across all three letters was 2.3 words per minute. Performance with semantically defined categories was substantially better, as he generated an average of 12.3 items per minute, with a range of 6 to 18.

On another occasion, a word was provided, and the patient was asked to generate as many rhyming words as possible in 1 minute. A total of five words were presented. He produced an average of 2.0 rhyming words per minute; he did not produce nonrhyming words. Age- and education-matched controls, in contrast, generated an average of 8.4 words per minute.

In an effort to demonstrate that the diminished fluency reflected a specifically verbal impairment, a nonverbal analog of the Thurstone Word Fluency Test was administered in which the patient was asked to create as many different drawings in 4 minutes as possible using only four lines.[36] On two trials he created an average of 16 drawings, a performance that is within the normal range.

COMMENT

We have presented data derived from a 59-year-old man with a minor Broca's aphasia secondary to a documented left dorsolateral frontal lobe infarct who demonstrated a severe memory impairment of a type not previously described, to our knowledge. Evaluation of the patient's memory revealed that he was sensitive to distraction, did not demonstrate the normal release from proactive inhibition, showed an effect of recency but not primacy, and, perhaps most interestingly, exhibited a marked memory impairment for the encoding and/or retrieval of phonologically, compared with semantically, specified items. Several issues concerning this patient's performance warrant attention.

The first issue concerns the relationship between the patient's language capacities and his memory impairment. Abundant evidence suggests that both fluent and nonfluent aphasias may be associated with a verbal memory impairment. Might the patient's memory deficit be secondary to a subtle language deficit?

A number of specific mechanisms have been proposed to account for the impairments of short-term memory encountered in aphasic patients. The impaired verbal short-term memory encountered in a probable Wernicke aphasic, for example, has been attributed to a failure to generate an adequate phonological representation[37]; the impairment seen in certain conduction aphasics has been attributed to a pathologic reduction in the capacity of the short-term store[38,39]; finally, in certain Broca's aphasics, the impairment of short-term memory has been attributed to failure of repetition, with a resultant failure of rehearsal in the putative articulatory loop.[15,40]

None of these proposed explanations, however, can account for the data derived from our patient. Our patient exhibited no demonstrable phonological impairment on tests of auditory comprehension, phoneme discrimination, and rhyme judgment. Additionally, our patient had no impairment of repetition and, as indicated by his perfect performance on the Peterson and Peterson[28] task with an unfilled delay, was able to retain phonologically encoded data, presumably by means of rehearsal within the articulatory loop.

Because the patient's infarct involves Broca's area, a brain region thought to be important in the control of motor aspects of speech production, one might suggest that the memory deficit reflects an impairment at the level of motor programming for speech. There are several lines of evidence that make this possibility seem unlikely. The patient's spontaneous speech demonstrates only a minimal abnormality—occasional word-finding problems—that might be attributed to an impairment of the motor programmer. Additionally, this hypothesis provides no principled account of the dissociation between the retrieval of phonologically, compared with semantically, guided retrieval. Finally, a deficit with phonologically cued stimuli was documented on the levels of processing task in which no verbal output was necessary.

A second issue concerns the marked dissociation between the patient's normal phonological processing in naturalistic, "automatic" language tasks such as spontaneous speech, reading, and naming and his marked impairment on memory and fluency tasks requiring the strategically guided, "controlled" retrieval of phonologically specified items. Following Schneider and Shiffrin[41] and Shiffrin and Schneider[42], a controlled process refers to an attention-requiring procedure that may be accessed or developed for the completion of a novel or unusual task. Tasks such as the production of lists of rhyming words that are not part of normal language routines may require a strategically guided or controlled search of lexical phonology. An automatic process, in contrast, is effortless and proceeds without active control; the semantically guided activation of lexical phonology that is thought to characterize normal routines involved in speech production[43] and object naming may involve an automatic process.

Within this framework, one possible explanation for the patient's deficits is an impairment in the controlled search of stored information. This hypothesis may take at least two forms. First, one might propose that the deficit is specific to the domain of lexical phonology; in this hypothesis, the controlled search of lexical semantics is assumed to be normal. Because tasks such as the retrieval of phonology on the basis of rhyme or initial letter are assumed to require controlled search of phonological information, whereas spontaneous speech, naming repetition, and reading are assumed to be mediated by the relatively automatic procedures involved in normal speech production, this hypothesis can account for the patient's performance.

A second explanation is that the patient suffers from a general impairment in controlled search. On this hypothesis, the difference in performance between phonologically and semantically specified items might reflect differences in the amount of effort required for controlled searches of the semantic and phonological stores, which, in turn, may reflect discrepancies in the organization of these stores; an impaired procedure for controlled search may be more effective operating within the semantic domain, in which related items may be "linked," compared with phonological stores, in which such interrelationships are weak or absent. One might expect, for example, that the retrieval of animal names would be facilitated by the multiplicity of semantic and, perhaps, visual attributes that they share; in contrast, preexisting linkages between words sharing an initial letter in the phonological lexicon would be expected to be weak.

The hypothesis that the patient's symptoms reflect an impairment in controlled search of stored information also accounts for another interesting aspect of his performance: the relatively normal recency effect, but the failure to demonstrate primacy. Recency effects are typically attributed to the maintenance of phonological information in the articulatory loop or phonemic buffer; primacy effects, in contrast, are typically attributed to the activation of lexical information. Thus, the ability to produce words from the beginning of a list (ie, primacy) may require the controlled search of lexical phonology, which, in our hypothesis, is assumed to be impaired.

Anatomic studies in monkeys provide data consistent with the proposal that the patient's dorsolateral frontal lobe infarct is associated with a defect in the controlled search of lexical phonology. Chavis and Pandya,[44] for example, demonstrated that the frontal lobes (including the dorsolateral, medial, and orbitofrontal portions) have reciprocal connections with the primary auditory and auditory association cortex. One might speculate that the left dorsolateral frontal lobe plays a critical role in the retrieval of lexical phonology by virtue of its role in the activation of the auditory association cortex (including Wernicke's area), which may support lexical phonology in man.

An important, but thus far unanswered, question is whether the putative deficit in controlled search underlies the patient's memory impairment. Although one might expect a general deficit in controlled search of stored information to cause a memory impairment, in the absence of an explicit account of the role of phonological factors in encoding and retrieval, it is not clear whether a specific impairment in the retrieval of phonologically specified information would cause amnesia. It is also possible, of course, that the impairment in controlled search and memory deficit are unrelated but co-occur because both processes are dependent on structures in the left dorsolateral frontal lobe.

An additional issue concerns the implications of our patient's performance for conceptions regarding the relationship between the frontal lobe and memory. Investigations involving monkeys[45,46] and man[47,48] have suggested that frontal lobe damage may be associated with specific memory impairments. Other researchers, however, have argued that the apparent memory failure observed with frontal lobe damage does not represent a specific impairment of encoding or retrieval but a disruption of more complex forms of human behavior.[9,29] Luria,[49] for example, argued that patients with frontal lobe damage are unable to maintain a stable intention to remember and are plagued by "pathologic inertia" and "high distractibility." In a similar vein, Warrington and Weiskranz[34] proposed that the frontal lobes play a critical role in the cognitive mediation mechanism, which serves to organize, manipulate, and embellish memory input. Signoret and Lhermitte[50] provided empirical support for the proposal that memory deficits associated with frontal lobe damage may be related to a deficit in the organization of material to be learned, rather than encoding or retrieval per se; these investigators described two patients with frontal lobe damage who were severely impaired in paired associate list learning but were relatively unimpaired when the stimuli were presented in a sentence context or with instructions to generate a visual image of the named objects.

Although the data derived our patient confirm previous observations that even relatively minor frontal lobe damage may be associated with a profound memory impairment, these data do not permit one to adjudicate between these possibilities. To the extent that the memory impairment is attributable to the putative deficit in controlled search of lexical phonology, the data support the thesis that frontal lobe amnesia is attributable to higher-level impairments rather than to impaired encoding or retrieval. Alternatively, if the memory deficit and impairment in controlled search are unrelated, the data may be consistent with the view that the frontal lobes are critical for encoding and/or retrieval.

Finally, one might wonder why the at least relatively selective impairment in processing of phonologically cued information demonstrated by our patient has not been reported previously. One possibility is that the impairment has been confounded by the frequent association of dorsolateral frontal lobe lesions with nonfluent aphasia; impairments in the motor aspects of speech production or lexical phonology, which are often observed in association with left dorsolateral frontal lobe infarcts, might obscure the effects of impairment in controlled search.

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References

1. Risse GL, Rubens AB, Jordan LS. Disturbances of long-term memory in aphasic patients. *Brain*. 1984;107:605-617.
2. DeRenzi E, Nichelli P. Verbal and nonverbal short-term memory impairment following hemispheric damage. *Cortex*. 1975;11:341-354.
3. Cermak LS, Butters N, Moreines J. Some analyses of the verbal encoding deficit of alcoholic Korsakoff patients. *Brain Lang*. 1974;1:141-150.
4. Cermak LS, Moreines J. Verbal retention deficits in aphasic and amnesic patients. *Brain Lang*. 1976;3:16-27.
5. Cermak LS, Stiassny D, Uhly B. Reconstructive retrieval deficits in Broca's aphasia. *Brain Lang*. 1984;21:95-104.
6. Mohr J, Pessin M, Finkelstein S, Funkenstein H, Duncan G, Davis G. Broca's aphasia: pathologic and clinical aspects. *Neurology*. 1978;28:311-324.
7. Foix C. Aphasies. In: Roger G, Widal P, Tessier PJ, eds. *Nouveau Traite de Medicine*. New York, NY: Masson Publishers USA Inc; 1928:223-246.
8. Milner B. Some effects of frontal lobectomy in man. In: Warren JM, Akert K, eds. *The Frontal Granular Cortex and Behavior*. New York, NY: McGraw-Hill International Book Co; 1964:313-334.
9. Benton AL. Differential behavioral effects in frontal lobe disease. *Neuropsychologia*. 1968;6:53-60.
10. Dunn LM. *Peabody Picture Vocabulary Test*. Circle Pines, Minn: American Guidance Service; 1959.
11. Kertesz A. *Aphasia and Related Disorders*. New York, NY: Grune & Stratton; 1979.
12. Goodglass H, Kaplan E. *Assessment of Aphasia and Related Disorders*. Philadelphia, Pa: Lea & Febiger; 1982.
13. DeRenzi E, Vignolo LA. The token test: a sensitive test to detect receptive disturbances in aphasia. *Brain*. 1962;85:665-678.
14. Kaplan E, Goodglass H, Weintraub S. *Boston Naming Test*. 1976. Experimental edition.
15. Heilman KM, Scholes R, Watson RT. Defects of immediate memory in Broca's and conduction aphasia. *Brain Lang*. 1976;3:201-208.
16. Gonzalez Rothi L, Coslett HB, Heilman KM. *Battery of Adult Reading Function*. 1983. Experimental edition.
17. Goodglass H, Gleason JB, Bernholtz NA, Hyde MR. Some linguistic structures in the speech of a Broca's aphasic. *Cortex*. 1972;8:191-212.
18. Berg EA. A simple objective test for measuring flexibility in thinking. *J Gen Psychol*. 1948;39:15-22.
19. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935;18:643-662.
20. Christensen A. *Luria's Neuropsychological Investigations*. Holliswood, NY: Spectrum Publications; 1981.
21. Wechsler D. A standardized memory scale for clinical use. *J Psychol*. 1945;19:87-95.
22. Taylor EM. *The Appraisal of Children with Cerebral Deficits*. Cambridge, Mass: Harvard University Press; 1959.
23. Milner B. Visual recognition and recall after right-temporal lobe excision in man. *Neuropsychologia*. 1968;6:191-209.
24. Kimura D. Right temporal lobe damage. *Arch Neurol*. 1963;8:48-56.
25. Huppert F, Piercy M. Recognition memory in amnesic patients: effect of temporal context and familiarity of material. *Cortex*. 1976;12:3-20.
26. Squire L. Two forms of human amnesia: an analysis of forgetting. *J Neurosci*. 1981;1:635-640.
27. Freed D, Corkin S, Cohen N. Forgetting in H.M.: a second look. *Neuropsychologia*. 1987;25:461-471.
28. Peterson LR, Peterson MJ. Short-term retention of individual verbal items. *J Exp Psychol*. 1959;58:193-198.
29. Butters N, Grady G. Effect of predistractor delays on the short-term memory performance of patients with Korsakoff's and Huntington's disease. *Neuropsychologia*. 1977;15:701-706.
30. Wickens DD. Encoding categories of words: an empirical approach to meaning. *Psychol Rev*. 1970;77:1-15.
31. Moscovitch M. Multiple dissociations of function in amnesia. In: Cermak L, ed. *Human Memory and Amnesia*. Hillsdale, NJ: Lawrence Erlbaum; 1982:337-370.
32. Freedman M, Cermak LS. Semantic encoding deficits in frontal lobe disease and amnesia. *Brain and Cognition*. 1986;5:108-114.
33. Craik FIM, Lockhart RS. Levels of processing. A framework for memory research. *J Verbal Learn Verbal Behav*. 1972;11:671-684.
34. Warrington EK, Weiskranz L. Amnesia: a disconnection syndrome? *Neuropsychologia*. 1982;20:233-248.
35. Benton AL, Hamsher KD. *Multilingual Aphasia Examination*. Iowa City, Iowa: University of Iowa; 1976.
36. Jones-Gotman M, Milner B. Design fluency: the investion of nonsense drawings after focal cortical lesions. *Neuropsychologia*. 1977;15:653-674.
37. Caramazza A, Berndt RS, Basili AG. The selective impairment of phonological processing: a case study. *Brain Lang*. 1983;18:128-174.
38. Shallice T, Warrington EK. Auditory-verbal short-term memory impairment and conduction aphasia. *Brain Lang*. 1977;4:479-491.
39. Caramazza A, Basili AG, Koller JJ, Berndt RS. An investigation of repetition and language processing in a case of conduction aphasia. *Brain Lang*. 1981;14:235-271.
40. Martin RC. Articulatory and phonological deficits in short-term memory and their relation to syntactic processing. *Brain Lang*. 1987;32:159-192.
41. Schneider W, Shiffrin RM. Controlled and automatic human information processing, I: detection, search and attention. *Psychol Rev*. 1977;84:1-66.
42. Shiffrin RM, Schneider W. Controlled and automatic human information processing, II: Perceptual learning, automatic attending and a general theory. *Psychol Rev*. 1977;84:127-189.
43. Garrett M. Levels of processing in sentence production. In:Butterworth B, ed. *Language Production*. London, England: Academic Press; 1980:177-220.
44. Chavis DA, Pandya DN. Further observations on corticofrontal connections in the rheusus monkey. *Brain Res*. 1976;117:369-386.
45. Gross CG, Weiskranz L. Some changes in behavior produced by lateral frontal lesions in the macaque. In: Warren JM, Akert K, eds. *The Frontal Granular Cortex and Behavior*. New York, NY:McGraw-Hill International Book Co; 1964:74-101.
46. Mishkin M, Vest B, Waxler M, Rosvold HE. A re-examination of the effects of frontal lesions on object alternation. *Neuropsychologia*. 1969;7:357-363.
47. Alexander M, Freedman M. Amnesia after anterior communicating artery aneurysm rupture. *Neurology*. 1984;34:752-757.
48. Volpe B, Hirst W. Amnesia following rupture and repair of an anterior communicating artery aneurysm. *J Neurol Neurosurg Psychiatry*. 1983;46:704-709.
49. Luria A. Memory disturbance in local brain lesions. *Neuropsychologia*. 1971;9:367-375.
50. Signoret J, Lhermitte F. Amnesic syndromes and the encoding process. In: Rosenzweig MR, Bennett EL, eds. *Neural Mechanisms of Learning and Memory*. Cambridge, Mass: MIT Press; 1976:67-75.

Rapid Recovery From Cortical Visual Impairment Following Correction of Prolonged Shunt Malfunction in Congenital Hydrocephalus

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• Three children with congenital hydrocephalus are described in whom increased intracranial pressure was associated with severe, long-lasting cortical visual impairment. Following shunt revisions or reconstructive craniotomies, visual improvement began within hours. It is speculated that increased intracranial pressure can occasionally result in chronic hypoperfusion of the parietal-occipital lobes, either due to posterior cerebral artery compromise secondary to transtentorial pressure gradient or to direct compression of cerebral tissues.

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Increased intracranial pressure (ICP) caused by shunt malfunction in the treatment of hydrocephalus can occasionally damage the visual pathways.[1] Various mechanisms have been suggested to explain the visual loss. Anterior visual pathway injury can occur from ischemia secondary to papilloedema[2] or from a markedly dilated third ventricle, which presses on the chiasm[3]; and it is also possible for the optic tracts to be compressed by the tentorial edge during herniation of the hippocampus.[4] Damage to the striate cortex and/or optic radiation can cause cortical visual impairment. This is much more likely to be transient than permanent in children who have experienced shunt failures,[5,6] but the recovery of vision tends to be slow, sometimes over a period of 3 to 5 years. In shunt failure the most common mechanism of permanent visual impairment is infarction of the occipital lobes resulting from occlusion of the posterior cerebral arteries during tentorial herniation,[1] but even in these children some degree of visual recovery is common.

We describe three children with congenital hydrocephalus in whom increased ICP was associated with severe, prolonged cortical visual impairment. However, improvement in vision began within hours following the shunt revision. Since 1984, we have studied more than 200 children with severe cortical visual impairment[1,7-9] who were referred to our visually impaired program. This type of quick improvement from prolonged visual loss related to increased ICP, although not complete recovery, in two of the children is most unusual and we have not seen it described in the literature. The possible pathophysiology is described.

REPORT OF CASES

CASE 1.—A female infant was born at 39 weeks' gestation with a thoracolumbar meningomyelocele after a normal pregnancy. Computed tomographic scan showed Chiari II malformation with markedly dilated ventricles. The spinal defect was closed and a ventriculoperitoneal shunt was inserted in the neonatal period. At 2.5 months the shunt was revised because of malfunction. The infant was noted to have been blind since birth, although the full eye examination was normal. She was totally oblivious to her environment. She did not blink to threat and did not follow or look at bright lights. The eye movements were normal. In contrast, she responded to sounds and smiled to her parents' voices. Due to continued shunt malfunction, she had another revision at 4 months of age. Within hours, her sight rapidly began to improve and 2 months later her caregivers felt that her vision was normal. At 4.5 years of age, the neurologic evaluation revealed paraplegia and absent deep tendon reflexes in the lower extremities. The tone was minimally increased in the arms and her hand movements were slightly tremulous. The ophthalmologic examination, including visual acuity 20/20, remained normal. Her intellectual development was age appropriate. Repeated computed tomographic scans showed that the shunt was functioning and visual-evoked potential studies (VEP) showed no abnormalities.

CASE 2.—A male infant was born at 36 weeks' gestation after a normal pregnancy. Hydrocephalus was diagnosed shortly before birth and cephalocentesis was performed. He was delivered by elective cesarean section. Ventriculoperitoneal shunt surgery was performed early in the neonatal period. His computed tomographic scan revealed dilated ventricles, aqueductal stenosis with a corpus callosum abnormality, and migration defects around the sylvian fissures. Although his ocular examination was normal, he had been totally blind since birth. He did not look at bright lights or follow them. He completely ignored his environment visually, although he responded to the voices of his parents. His eye movements were normal, without evidence of nystagmus. At 5 months of age, increased ICP was diagnosed and his shunt was repaired. Within 48 hours his vision rapidly improved to the point where he could follow objects 2 to 3 feet away, but he remained visually inattentive.

At 2 years of age he still had visual inattentiveness and variable vision. His ocular examination remained normal, but measuring his distance visual acuity was impossible because the preferential looking tests suitable for preverbal or multihandicapped children were still not available to us. His development was delayed and he began to have seizures. At age 3.5 years his shunt was still functioning and he was seizure free. His visual acuity, tested by preferential looking tests, was 9.8 cycle per degree, which approximates 20/50 in Snellen measurements.

CASE 3.—A male infant was born at term after a normal pregnancy. An emergency cesarean section was performed because of prolonged labor and fetal distress. The infant was resuscitated. He was noted to have a high lumbar meningomyelocele with paraplegia and hydrocephalus that required ventriculoperitoneal shunting. Computed tomographic scan revealed Chiari II malformation with markedly dilated ventricles. Although his full ocular examination was normal, in his early infancy he completely ignored his visual environment. He did not blink to bright light or to threat. In contrast, he responded to his parents' voices and seemed to enjoy music.

The total blindness persisted until 7 months of age, when a diagnosis of progressive sagittal synostosis was made and corrective surgery was performed. Within 2 to 3 days his vision began to improve, he reached for objects, and a few weeks later he appeared to recognize his parents from across the room. At 10 months of age he was using his sight much more but he was still believed to be visually inattentive.

At the age of 6.5 years, over a period of 4 to 5 months, he gradually lost his vision. Again he became oblivious to his environment visually, but continued to talk. Investigations revealed increased ICP, secondary to small intracranial volume although the shunt was functioning. Reconstructive biparietal craniotomies were performed. Within 48 hours his sight dramatically improved and a few days later his distance Snellen acuity was 20/40 in the left eye and 20/70 in the right eye. At the age of 8 years his vision was the same as before, the funduscopic examination was normal, but on confrontation he appeared to have minimal bilateral peripheral visual loss. He was fully integrated in school, but received learning assistance. He was noted to

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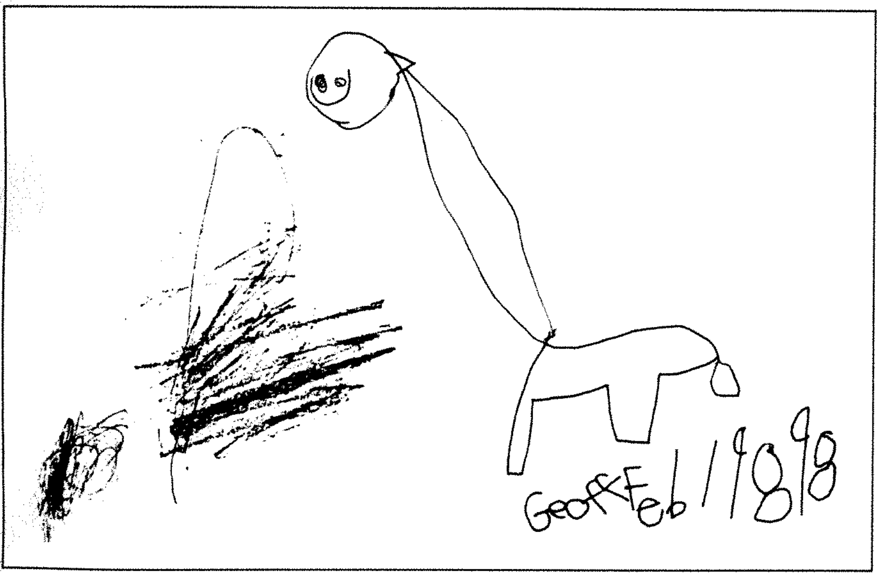

The changes in the drawing abilities of patient 3. On the left note the infantile drawing skills during shunt malfunction and on the right the improvement a few days after shunt repair.

be visually inattentive with variable visual function. Psychological testing revealed significant visual perceptual difficulties.

A few months later, his shunt malfunctioned and he began to lose his sight. His teacher observed profound deterioration in his visual skills, his drawing regressed to an infantile state, whereas his verbal abilities and his coordination changed only minimally. However, he frequently gave answers that bore no relationship to the questions. He was referred to an ophthalmologist who did not note any abnormal ocular findings, but found the distance visual acuity to be inconsistent and at best to be 20/200 with correction. The shunt was repaired, and within a couple of days the distance acuity was 20/40 in the left eye and 20/100 in the right eye. His visual-perceptual skills greatly improved (Figure). The neurologic evaluation still showed paraplegia, minimal bilateral peripheral visual field loss on kinetic arc perimetry, and the funduscopic examination remained normal. The VEP and VEP map studies performed postoperatively were also normal.

Due to episodes of increased ICP, this child lost his vision temporarily on two separate occasions. Although the distance visual acuity and visual functioning dramatically improved after surgery, both parents and teachers believed that on each occasion some permanent loss occurred in his visual-perceptual skills. Psychological evaluation substantiated this impression and showed multiple learning disabilities, with visual-perceptual skills being affected the most severely.

COMMENT

These children were born with hydrocephalus. In cases 1 and 3 the diagnosis was meningomyelocele and Chiari II malformation, in case 2 the diagnosis was aqueductal stenosis with congenital anomalies of the brain. The children appeared to be blind from birth until the chronically increased ICP was corrected, and then visual improvement was noted within hours. The process was repeated on three separate occasions in the third child.

The cause of visual impairment was believed to be a disturbance of the visual cortex and optic radiation in all three children. Their eye examinations were always normal. The computed tomographic scans, during shunt failures, revealed markedly dilated occipital horns.

It is known that the latency and amplitude of the VEP components are altered in patients with treated hydrocephalus and those with shunt malfunction.[10] These alterations may be due to papilloedema,[11] anterior pathway compression,[12] stretching of the posterior optic radiation by the enlarged ventricles, or hemisphere ischemia. Abnormalities in the VEP when associated with ventriculomegaly are more obvious with increased ICP.[10] Following shunting or revision, VEPs tend to return to their pretreatment state. Recovery may occur within a few days of treatment or may be more delayed. However, such quick clinical visual improvement after the relief of increased ICP as seen in our cases is unusual because children with various types of long-standing cortical visual impairment tend to regain their sight gradually.[7-9]

The rapid visual improvement seen in these patients suggests that the pathophysiology of blindness might have been prolonged hypoperfusion of the parieto-occipital lobes from chronically increased ICP. This may have been due to posterior cerebral artery compromise secondary to a transtentorial pressure gradient or to direct compression of cerebral tissues. With relief of increased ICP, perfusion to the parieto-occipital areas was reestablished and as a result vision and visual perceptual skills rapidly improved. The visual loss in our patients was severe. It is possible that increased ICP can cause milder forms of visual dysfunction more frequently than apparent, but these children were not referred to clinics or agencies working with the blind and their visual functions were not tested. It is also important to emphasize that long-standing neurologic deficits can be reversed with appropriate control of elevated intracranial pressure.

Most of the children with shunt failures or increased ICP are too sick and/or too young to cooperate with the various Snellen vision charts. On the other hand, the recent introduction of preferential looking or grading acuity tests,[13] which are based on pattern preference, appear to be much more feasible since they require little or no verbal communication.

References

1. Arroyo HA, Jan JE, McCormick AQ, Farrell K. Permanent visual loss after shunt malfunction. *Neurology.* 1985;35:25-29.
2. Hayreh SS. Optic disk edema in raised intracranial pressure, VI: associated visual disturbances and their pathogenesis. *Arch Ophthalmol.* 1977;95:1566-1579.
3. Walsh FB, Hoyt WF. *Clinical Neuro-ophthalmology.* Baltimore, Md: Williams & Wilkins; 1964;1:1-129.
4. Meyer A. Herniation of the brain. *Arch Neurol Psychiatry.* 1920;4:387-400.
5. Lorber J. Recovery of vision following prolonged blindness in children with hydrocephalus or following pyogenic meningitis. *Clin Pediatr.* 1967;6:699-703.
6. Smith JL. Cortical blindness in congenital hydrocephalus. In: Smith JL, ed. *Neuro-ophthalmology.* St Louis, Mo: Mosby–Year Book; 1967;3:211-217.
7. Whiting S, Jan JE, Wong PKH, Flodmark O, Farrell K, McCormick AQ. Permanent cortical visual impairment in children. *Dev Med Child Neurol.* 1985;27:730-739.
8. Flodmark O, Jan JE, Wong PKH. Computed tomography of the brain in children with cortical visual impairment. *Dev Med Child Neurol.* 1990;32:611-620.
9. Lambert SR, Hoyt CS, Jan JE, Barkovich J, Flodmark O. Visual recovery from hypoxic cortical blindness during childhood: computed tomographic and magnetic resonance imaging predictors. *Arch Ophthalmol.* 1987;105:1371-1377.
10. Coupland SG, Cochrane DD. Visual evoked potentials, intracranial pressure and ventricular size in hydrocephalus. *Doc Ophthalmol.* 1987;66:321-330.
11. Kirkham TH, Coupland SG. Abnormal electroretinograms and visual evoked potentials in chronic papilledema using time-difference analysis. *Can J Neurol Sci.* 1981;8:243-248.
12. Halliday AM, Halliday E, Kriss A. The pattern-evoked potential in compression of the anterior visual pathways. *Brain.* 1976;99:357-374.
13. Van Hof-van Duin J. The development and study of visual acuity. *Dev Med Child Neurol.* 1981;31:543-552.

TRIGGERS MIGRAINE*

激發偏頭痛

ABORTS MIGRAINE

抑制偏頭痛

Cafergot®

(ergotamine tartrate and caffeine) Tablets/Suppositories

- Highly Effective:
  Aborts migraines before they start
  Stops migraines in progress
- Reliable and Predictable

The choice from the start

*MSG, a common additive in Chinese cooking, may precipitate migraine attacks in susceptible individuals.

Please see following page for brief summary of prescribing information.

SANDOZPHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

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Cafergot®

(ergotamine tartrate and caffeine) tablets, USP
(ergotamine tartrate and caffeine) suppositories, USP

DESCRIPTION

Cafergot® (ergotamine tartrate and caffeine) Tablet

ergotamine tartrate USP	1 mg
caffeine USP	100 mg

Inactive Ingredients: acacia, carnauba wax, lactose, methylparaben, povidone, propylparaben, sodium benzoate, sorbitol, starch, stearic acid, sucrose, synthetic black ferric oxide, synthetic red ferric oxide, synthetic yellow ferric oxide, talc, tartaric acid, and titanium dioxide.

Cafergot® (ergotamine tartrate and caffeine) Suppository

ergotamine tartrate USP	2 mg
caffeine USP	100 mg

Inactive Ingredients: cocoa butter NF and tartaric acid NF.

Cafergot® (ergotamine tartrate and caffeine) suppositories are *sealed* in foil to afford protection from cocoa butter leakage. If an unavoidable period of exposure to heat softens the suppository, it should be chilled in ice-cold water to solidify it before removing the foil.

ACTIONS: Ergotamine is an alpha adrenergic blocking agent with a direct stimulating effect on the smooth muscle of peripheral and cranial blood vessels and produces depression of central vasomotor centers. The compound also has the properties of serotonin antagonism. In comparison to hydrogenated ergotamine, the adrenergic blocking actions are less pronounced and vasoconstrictive actions are greater.

Caffeine, also a cranial vasoconstrictor, is added to further enhance the vasoconstrictive effect without the necessity of increasing ergotamine dosage.

Many migraine patients experience excessive nausea and vomiting during attacks, making it impossible for them to retain any oral medication. In such cases, therefore, the only practical means of medication is through the rectal route where medication may reach the cranial vessels directly, evading the splanchnic vasculature and the liver.

INDICATIONS

Cafergot® (ergotamine tartrate and caffeine)

Indicated as therapy to abort or prevent vascular headache, e.g., migraine, migraine variants or so-called "histaminic cephalalgia".

CONTRAINDICATIONS: Peripheral vascular disease, coronary heart disease, hypertension, impaired hepatic or renal function, sepsis and pregnancy.

Hypersensitivity to any of the components.

PRECAUTIONS: Although signs and symptoms of ergotism rarely develop even after long term intermittent use of the orally or rectally administered drugs, care should be exercised to remain within the limits of recommended dosage.

Ergotism is manifested by intense arterial vasoconstriction, producing signs and symptoms of peripheral vascular ischemia. Ergotamine induces vasoconstriction by a direct action on vascular smooth muscle. In chronic intoxication with ergot derivatives, headache, intermittent claudication, muscle pains, numbness, coldness and pallor of the digits may occur. If the condition is allowed to progress untreated, gangrene can result.

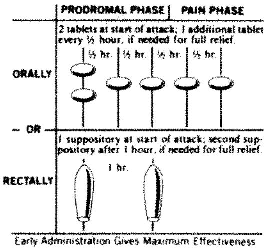
While most cases of ergotism associated with ergotamine treatment result from frank overdosage, some cases have involved apparent hypersensitivity. There are few reports of ergotism among patients taking doses within the recommended limits or for brief periods of time. In rare instances, patients, particularly those who have used the medication indiscriminately over long periods of time, may display withdrawal symptoms consisting of rebound headache upon discontinuation of the drug.

There have been reports of drug abuse and psychological dependence in patients on Cafergot® (ergotamine tartrate and caffeine) therapy. Due to the chronicity of vascular headaches, it is imperative that patients be advised not to exceed recommended dosages with long-term use to avoid ergotism.

ADVERSE REACTIONS: Vasoconstrictive complications, at times of a serious nature, may occur. These include pulselessness, weakness, muscle pains and paresthesias of the extremities and precordial distress and pain. Although these effects occur most commonly with long-term therapy at relatively high doses, they have also been reported with short-term or normal doses. Other adverse effects include transient tachycardia or bradycardia, nausea, vomiting, localized edema and itching.

DOSAGE AND ADMINISTRATION

Procedure: For the best results, dosage should start at the first sign of an attack.


PRODROMAL PHASE
PAIN PHASE
2 tablets at start of attack; 1 additional tablet every ½ hour, if needed for full relief.
½ hr.
½ hr.
½ hr.
½ hr.
ORALLY
— OR
1 suppository at start of attack; second suppository after 1 hour, if needed for full relief.
1 hr.
RECTALLY

Early Administration Gives Maximum Effectiveness

MAXIMUM ADULT DOSAGE

Orally: Total dose for any one attack should not exceed 6 tablets.

Rectally: Two suppositories is the maximum dose for an individual attack.

Total weekly dosage should not exceed 10 tablets or 5 suppositories.

In carefully selected patients, with due consideration of maximum dosage recommendations, administration of the drug at bedtime may be an appropriate short-term preventive measure.

OVERDOSAGE: The toxic effects of an acute overdosage of Cafergot® (ergotamine tartrate and caffeine) are due primarily to the ergotamine component. The amount of caffeine is such that its toxic effects will be overshadowed by those of ergotamine. Symptoms include vomiting, numbness, tingling, pain and cyanosis of the extremities associated with diminished or absent peripheral pulses; hypertension or hypotension; drowsiness, stupor, coma, convulsions and shock. A case has been reported of reversible bilateral papillitis with ring scotomata in a patient who received five times the recommended daily adult dose over a period of 14 days.

Treatment consists of removal of the offending drug by induction of emesis, gastric lavage, and catharsis. Maintenance of adequate pulmonary ventilation, correction of hypotension, and control of convulsions are important considerations. Treatment of peripheral vasospasm should consist of warmth, but not heat, and protection of the ischemic limbs. Vasodilators may be used with benefit but caution must be exercised to avoid aggravating an already existent hypotension.

HOW SUPPLIED

Cafergot® (ergotamine tartrate and caffeine) Tablets

Shell pink colored, sugar coated, imprinted "CAFERGOT" on one side, "S" on other side. Bottles of 250, NDC 0078-0034-28, and cartons of three SigPak® (dispensing unit) packages, each containing 30 tablets in individual blisters, NDC 0078-0034-42.

Cafergot® (ergotamine tartrate and caffeine) Suppositories

Sealed in fuchsia-colored aluminum foil, imprinted "S CAFERGOT® SUPPOSITORY 78-33 SANDOZ". Boxes of 12, NDC 0078-0033-02.

[DECEMBER 1, 1990 CAF-Z26]

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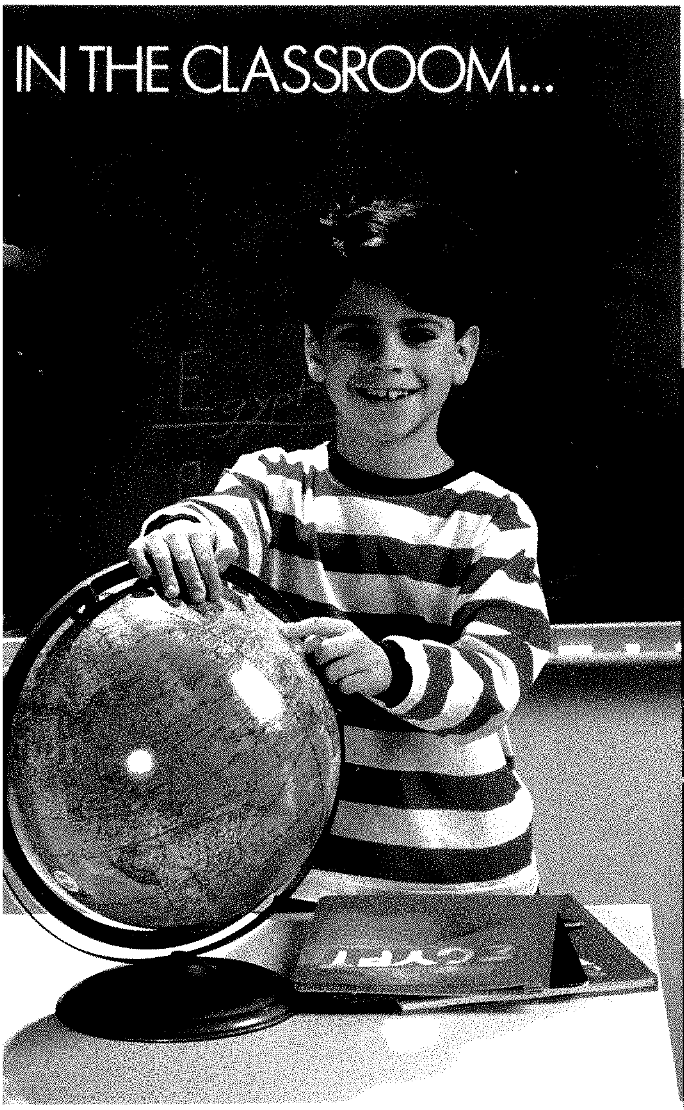
Seizures controlled, thoughts clear, smiles bright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Low risk of cognitive impairment[1]

Generally avoids hirsutism[2,3]

Avoids gingival hyperplasia[2,3]

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Tegretol® 200 mg scored tablets
100 mg chewable tablets

carbamazepine USP

...because after seizure control, there's a lot of living to do!

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the next page, especially the boxed warning.

References

1. Smith DB, Mattson RH, Cramer JA et al Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia* 1987;28(suppl 3):S50-S58.
2. Mattson RH, Cramer JA, Collins JF et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures *N Engl J Med* 1985;313:145-151
3. Herranz JL, Armijo JA, Arteaga R Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children *Epilepsia* 1988;29:794-804

Tegretol®

carbamazepine USP

Chewable Tablets of 100 mg—red-speckled, pink   Tablets of 200 mg—pink

WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

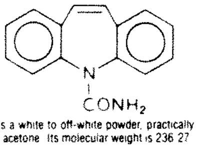
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone Its molecular weight is 236 27

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch stearic acid, and sucrose (chewable tablets only)

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures It appears to act by reducing polysynaptic responses and blocking the post-tetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia The mechanism of action remains unknown

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets Tegretol in blood is 76% bound to plasma proteins Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug Usual adult therapeutic levels are between 4 and 12 μg/ml Following oral administration, serum levels peak at 4 to 5 hours The CSF/serum ratio is 0 22, similar to the 22% unbound Tegretol in serum Because Tegretol may induce its own metabolism, the half-life is also variable Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types

1 Partial seizures with complex symptomatology (psychomotor, temporal lobe) Patients with these seizures appear to show greater improvement than those with other types
2 Generalized tonic-clonic seizures (grand mal)
3 Mixed seizure patterns which include the above, or other partial or generalized seizures

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General)

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia

Beneficial results have also been reported in glossopharyngeal neuralgia

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol These reactions have been extremely rare However, a few fatalities have been reported

Tegretol has shown mild anticholinergic activity, therefore, patients with increased intraocular pressure should be closely observed during therapy

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE)

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage and should be advised to report to the physician immediately if any such signs or symptoms appear

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used

Thyroid function tests have been reported to show decreased values with Tegretol administered alone

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone or a combination of two produces a marked lowering of serum levels of Tegretol The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene isoniazid or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected

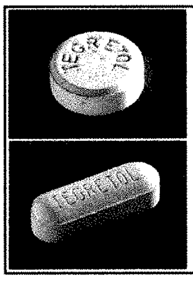
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75 and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results The significance of these findings relative to the use of carbamazepine in humans is at present, unknown

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate 1 talipes, 1, anophthalmos, 2) In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg

There are no adequate and well-controlled studies in pregnant women Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus

Retrospective case reviews suggest that compared with monotherapy there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy Therefore, monotherapy is recommended for pregnant women



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug taking into account the importance of the drug to the mother

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended

The following additional adverse reactions have been reported

Hemopoietic System Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria

Skin Pruritic and erythematous rashes urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia and diaphoresis In certain cases, discontinuation of therapy may be necessary

Cardiovascular System Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis and adenopathy or lymphadenopathy

Some of these cardiovascular complications have resulted in fatalities Myocardial infarction has been associated with other tricyclic compounds

Liver Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis

Respiratory System Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia

Genitourinary System Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence Albuminuria, glycosuria elevated BUN and microscopic deposits in the urine have also been reported

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher Relevance of these findings to humans is unknown

Nervous System Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established

Digestive System Nausea, vomiting gastric distress and abdominal pain, diarrhea, constipation anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis

Eyes Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes

Musculoskeletal System Aching joints and muscles, and leg cramps

Metabolism Fever and chills Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests)

Other Isolated cases of a lupus erythematosus-like syndrome have been reported There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants

A case of aseptic meningitis accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications The patient was successfully dechallenged and the meningitis reappeared upon rechallenge with carbamazepine

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol nor is there evidence of psychological or physical dependence in humans

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose adults >60 g (39-year-old man) Highest known doses survived adults, 30 g (31-year-old woman), children 10 g (6-year-old boy) small children, 5 g (3-year-old girl)

Oral LD50 in animals (mg/kg) mice, 1100-3750 rats, 3850-4025 rabbits 1500-2680 guinea pigs 920

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours Neuromuscular disturbances are the most prominent Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested

Respiration Irregular breathing respiratory depression

Cardiovascular System Tachycardia, hypotension or hypertension, shock conduction disorders

Nervous System and Muscles Impairment of consciousness ranging in severity to deep coma Convulsions especially in small children Motor restlessness muscular twitching tremor, athetoid movements, opisthotonos ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism psychomotor disturbances, dysmetria initial hyperreflexia followed by hyporeflexia

Gastrointestinal Tract Nausea, vomiting

Kidneys and Bladder Anuria or oliguria, urinary retention

Laboratory Findings Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria EEG may show dysrhythmias

Combined Poisoning When alcohol tricyclic antidepressants barbiturates or hydantoins are taken at the same time the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug which may be achieved by inducing vomiting irrigating the stomach, and by taking appropriate steps to diminish absorption If these measures cannot be implemented without risk on the spot the patient should be transferred at once to a hospital while ensuring that vital functions are safeguarded There is no specific antidote

Elimination of the Drug Induction of vomiting

Gastric lavage Even when more than 4 hours have elapsed following ingestion of the drug the stomach should be repeatedly irrigated especially if the patient has also consumed alcohol

Measures to Reduce Absorption Activated charcoal, laxatives

Measures to Accelerate Elimination Forced diuresis

Dialysis is indicated only in severe poisoning associated with renal failure Replacement transfusion is indicated in severe poisoning in small children

Respiratory Depression Keep the airways free, resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen

Hypotension Shock Keep the patient's legs raised and administer a plasma expander If blood pressure fails to rise despite measures taken to increase plasma volume use of vasoactive substances should be considered

Convulsions Diazepam or barbiturates

Warning Diazepam or barbiturates may aggravate respiratory depression (especially in children) hypotension and coma However barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week)

Surveillance Respiration, cardiac function (ECG monitoring), blood pressure body temperature pupillary reflexes and kidney and bladder function should be monitored for several days

Treatment of Blood Count Abnormalities If evidence of significant bone marrow depression develops, the following recommendations are suggested (1) stop the drug, (2) perform daily CBC platelet and reticulocyte counts (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery

Special periodic studies might be helpful as follows (1) white cell and platelet antibodies (2) 59Fe—ferrokinetic studies (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels

A fully developed aplastic anemia will require appropriate intensive monitoring and therapy, for which specialized consultation should be sought

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests) Dosage should be adjusted to the needs of the individual patient A low initial daily dosage with a gradual increase is advised As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level Tablets should be taken with meals

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b i d Increase at weekly intervals by adding up to 200 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age and 1200 mg daily in patients above 15 years of age Doses up to 1600 mg daily have been used in adults in rare instances ***Maintenance***: Adjust dosage to the minimum effective level, usually 800-1200 mg daily

Children 6-12 years of age—Initial: 100 mg b i d Increase at weekly intervals by adding 100 mg per day using a t i d or q i d regimen until the best response is obtained Dosage should generally not exceed 1000 mg ***Maintenance***: Adjust dosage to the minimum effective level usually 400-800 mg daily

Combination Therapy: Tegretol may be used alone or with other anticonvulsants When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C)

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b i d on the first day for a total daily dose of 200 mg This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain Do not exceed 1200 mg daily

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily However, some patients may be maintained on as little as 200 mg daily while others may require as much as 1200 mg daily At least once every 3 months throughout the treatment period attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 0028-0052-01
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0028-0052-61

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 0028-0027-01
Bottles of 1000	NDC 0028-0027-10
Gy-Pak*—One Unit 12 bottles—100 tablets each	NDC 0028-0027-65
Unit Dose (blister pack) Box of 100 (strips of 10)	NDC 0028-0027-61

Samples when available, are identified by the word *SAMPLE* appearing on each tablet

Protect from moisture

Dispense in tight container (USP)

Also available as Tegretol suspension 100 mg/5 ml, in 450 ml bottles

Printed in U S A   C90-34 (Rev 6 90)

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Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

A Translation of Otto Binswanger's Article, 'The Delineation of the Generalized Progressive Paralyses'

John P. Blass, MD, PhD; Siegfried Hoyer, MD; Roger Nitsch, MD

The task with which the esteemed committee of our society has charged me, that is, the introduction of the discussion on the definition of generalized progressive paresis by the characterization of the important aspects of the condition, can be divided into three parts: (1) consideration of the anatomic criteria, (2) the causes, and (3) the clinical course.

I shall attempt a brief examination of those of the characteristic features of progressive paresis that allow its differential diagnosis from other similar and related conditions, basing my considerations on all three of these aspects. I hope I may be allowed to observe, however, that the limited scope of this short report will allow me to do no more than give an imprecise indication of the clinical picture and that I hope a more exact representation of the whole or of individual parts of the whole will emerge from the discussion.

The first question, that of the anatomic characteristics of generalized progressive paresis, has been the subject of lively controversies, particularly in recent years. One needs only to recall the debates at the International Congress in Berlin, which most clearly reflect the fundamentally different opinions that still exist concerning this subject. I, myself, during the course of a more detailed treatment of the histologic findings, have lately attempted to delineate the primary impairments and to put forward their relationships to the tissue changes, which in the correct light appear to be secondary, insofar as these concern the cerebral cortex.

However, before we look at these anatomic details, which are still largely unexplained, we shall have to devote ourselves to the task of examining whether perhaps even the macroscopic postmortem findings alone offer us a way to discriminate progressive paresis unequivocally from other organic brain diseases.

The most important observations in the brain of a person with paresis are (1) reduction in brain weight; (2) atrophy of the cortex of the frontal and parietal lobes, the insular gyri, and the anterior portion of the temporal lobe; (3) expansion of the ventricles, internal hydrocephalus, and granular ependymitis; (4) external hydrocephalus, generalized brain edema, and chronic leptomeningitis; and (5) hemorrhagic pachymeningitis. (Changes in the substance of the spinal cord are deliberately not considered here, as they can hardly give rise to diagnostic errors in the assessment of anatomic findings. At most, it seems possible that in cases of tabetic paralysis, the less easily recognized macroscopic changes in the brain might be overlooked during the anatomic examination because of pronounced and unequivocal changes in the spinal cord. This is possible if the clinical signs and symptoms of the illness are unknown to the anatomist. The importance of spinal cord involvement in the pathologic process of progressive paresis has been described in articles published by Westphal and more recently by Fürstner.)

In the final picture of progressive paresis, we regularly find either all the postmortem findings listed herein in their entirety or at least some of them; nonetheless, no one should succumb to the temptation to come to either a positive or a negative conclusion on the basis of the presence or absence of only one of these features.

The first of the above observations that I intend to discuss are the changes attributable to leptomeningitis. Earlier, particularly under the influence of the work performed by Duchek and Meyer, the opinion prevailed that the meningitis-induced changes were actually the most obvious and, indeed, the primary pathologic processes in progressive paresis and, in accordance with this, that these changes were always present in the typical cases of this illness. Varied experience collected later, however, has proved that even in cases of long-standing progressive paresis, there is occasionally no evidence of any serious change attributable to meningitis. According to my own observations collected from patients in the clinic in Jena, among 106 postmortem examinations, 70 cases with pronounced leptomeningitis-induced changes were recorded, 28 with slight changes of this kind and eight with no sign whatsoever of such changes. In the cases with only slight involvement of the soft meninges, there were only intermittent whitish, cloudy areas or streaky thickenings along the greater vascular trunks. Similar observations are recorded in the brains of nonparetic individuals of the same age who have lived in similar circumstances. The extensive whitish, cloudy patches on the convex surface of the hemisphere, the fine granular grayish white and grayish-yellow deposits in the subarachnoid spaces, the plateletlike thickenings of the pia mater in the region of Magendi's foramen, the large transverse fissure of the brain, the optic chiasm, and the sylvian fissure are not present in these brains. The meninges can almost always be easily separated from the surface of the brain, with no superficial loss of substance; only at isolated points over the frontal lobe, especially over the gyrus rectus, we detach small particles from the glial coating and the uppermost layer of the cortex in the area of the incoming cortical vessels together with the pia mater. If even slight brain edema is present, extending the epicerebral spaces, these adhesions are also not observed. We deduce from this that there are very definitely pronounced cases of progres-

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sive paresis in which the so-called characteristic leptomeningitic changes are present only to a very slight degree or not at all.

The reduction in brain weight is regarded as the second most characteristic feature. It is certainly true that we shall be able to show quite a considerable reduction in the average brain weight (by 100 g and more) in the overwhelming majority of brains from elderly patients, especially if we have taken away the ventricular fluid and the edematous meninges. Nonetheless, I should like to pronounce a caveat against the assumption that every case of progressive paresis that has marked clinical features and is observed in an elderly patient must be accompanied by a reduction of this degree in brain weight. I have seen a number of unequivocal cases of progressive paresis in which death had supervened in the terminal stage and in which no substantial reduction in the brain weight was present. The volume of the brain should always be considered in conjunction with the overall body height and weight before a correct estimate of the average weight appropriate to the particular brain can be made. (A more detailed compilation of the macroscopic postmortem findings recorded in studies of patients who died with paresis from 1882 to 1894 in the clinic in Jena is to be published shortly by a colleague and former student of mine.)

There is another feature that is just as variable and unreliable: macroscopically visible atrophy of the cerebral cortex. For my present purposes, I disregard the generally familiar typical findings with widely yawning sulci and the narrowing of the frontal lobe gyri to narrow ridges, as these preclude difficulties when the diagnosis is made. Besides these findings, there are others, including the high-grade mental deterioration progressing over years of illness to complete devastation, which is in stark contrast to the macroscopically apparent destruction of specific cortical tissue. One is always newly surprised when neither examination of the brain surface nor the study of vertical sections of the hemispheres reveals demonstrable cortical atrophy. Of course, I am not thinking now of brains in which the cortical atrophy is obscured by a rather pronounced edematous saturation of the cerebral cortex and fissuring of the glia, often to a substantial degree (particularly in the second cortical layer and in the medullary lamina). (Unfortunately, no comprehensive measurements are available that could provide us with average values for the width of the cortex in the individual gyri. Even now, we therefore still have access only to extremely unreliable estimates, which mostly are of only very limited value to the observer. As yet, we are only in a position to recognize substantial wasting of the cortex; if this is not present in elderly patients with paresis, the interpretation of the degree of cortical atrophy varies widely among different examiners, as experience has shown me many times.)

If we recall the finer anatomic processes involved in the progression of the paretic condition, it becomes easy to understand that the destruction of the functional cortical tissue can be almost completely compensated for by reparatory proliferations of the connective tissue containing the vessels. This will be true particularly if the onset of the illness is at a relatively early age, while the glial tissue still has a very strong growth tendency.

With this, we come closer to the less numerous cases of diffuse brain sclerosis, which is known to be confined exclusively to childhood and early youth and has been described in some detail by Strümpell, Siemens, Schultze, Jendrassik, Marie, and others. This diffuse proliferation of the glial tissue, which substitutes for the specific neural tissue that has not developed completely, only rarely leads to pronounced thinning of the cerebral cortex. When cut through, the cortex is more likely to appear expanded and pale grayish white; an insight into the nature of the illness is not provided until the microscopic examination is performed. Confusion with progressive paresis will be possible when, on the one hand, following a long course of the illness, death does not occur until the patient is at an age at which the paretic condition is also pronounced, and, on the other hand, when the paretic condition occurs while the patient is still young. I refer you to the cases of juvenile paralysis reported in the psychiatric literature during the last two decades. In the second type of case mentioned above in particular, errors in diagnosis are probably not uncommon, as there is by no means a sharp discrimination between the clinical pictures of juvenile paralysis and diffuse cerebral sclerosis. A strict distinction can be made during an anatomic examination: diffuse cerebral sclerosis is characterized as a primary proliferation of the glial parts with simultaneous or rather earlier inhibition of the development of the neural elements (this glial proliferation can be explained by two different processes: [1] excessive growth of histologically unfinished ectodermal tissue components takes place or [2] the mesodermal parts of the connective tissue penetrating with the vessels show pathologically intensified growth and fill up the defects that have arisen as a consequence of the inhibited development of the ectodermal tissue); the paralysis presupposes the destruction of fully developed neural elements; and the glial proliferations in this case are secondary processes of repair. I am, of course, not unaware that this separation of the two pathologic processes—which is a scientific necessity—is countered by very considerable problems in practice when actual patients are examined.

Gliosis of the cerebral cortex, which was first reported by Fürstner, is more easily differentiated from paralysis. It has one feature that is completely peculiar to it, namely, the presence of tuberosities and granules extending beyond the surface of the brain and tending to form cavities in their interior. The only difference between this condition and diffuse sclerosis of the brain, I suppose, is its focal nature.

One of the most unequivocal features, in my opinion, is granular ependymitis. In my experience, this is never absent in progressive paresis. It must be mentioned that the granulations are not always very substantial. We find them occasionally only in the hindmost parts of the floor of the rhomboid fossa at the outermost border of the alae cinereae and at the lateral declivities of the roof of the fourth ventricle. Otherwise, they are most easily found at the outermost border of the strial callosities in the lateral ventricle.

I do not mean to say that these ependymal proliferations occur exclusively in the presence of general paresis. We encounter them occasionally in other organic brain diseases, particularly in the presence of brain tumors. I have also found distinct granular ependymitis in a few instances following so-called functional psychoses; these were in persons who had suffered from chronic paranoia and who had died at a fairly good age (between 50 and 60 years). There was certainly no relationship between this postmortem finding and the known psychosis; rather, it must be assumed that in these cases, complications are present as characterized by organic alterations in the brain that have superimposed themselves on the earlier pathologic process. Thus, we cannot say that the presence of granular ependymitis is an unmistakable sign of progressive paresis. In my opinion, however, the inverse of this conclusion is very well justified, namely, that if granular ependymitis is not present, the diagnosis of progressive paresis will be very dubious.

I have found it necessary to recognize the value of the macroscopically visible features of the postmortem findings in more detail, because in practice they are virtually the only basis for a diagnosis of paresis on the mortuary bench. In the case of forensic examinations, in particular, the conclusions drawn from these macroscopic observations can result in very important implications.

It can be inferred from the above discussion that the anatomic diagnosis of this illness is by no means confirmed by the presence of just one macroscopic finding that is also found in paresis. Anything more than the absence of one of the so-called typical alterations justifies its exclusion. The anatomic diagnosis, however, is ensured when several of these typical features are present simultaneously.

At our present state of knowledge, the microscopic examination poses many difficulties in diagnosis. In elderly patients in whom the macroscopically recognizable changes are distinctly pronounced, the microscopic examination also unequivocally shows the final results of chronically progressive wasting of the functional cortical tissue (wasting of the myelinated nerve fibers and destruction of the ganglion cells in places) in association with degenerative alterations in the vessel walls and reparatory formation of the interstitial tissue. In such circumstances, the first things to come to notice are hyaline degeneration and streaky thickening of blood vessels with endothelial proliferations; extravasations of blood and conglomerations of lymph corpuscles in the intravascular and extravascular lymphatic spaces, which are dilated in parts; rigid, thickened, fibrous interstitial tissue, especially in the outer layers of the cortex and in the glial coating; abundant astrocytes and so-called free nuclei; and leptomeningitic scars with proliferations and accumulations of nuclei within the endothelial membrane, while the nerve tissue defect cannot be established until more laborious comparative investigations are performed.

In the case of the so-called early forms, that is, in patients in whom both the onset and the course are chronic and who have died of intercurrent diseases during the initial stages of the paresis, as in the cases in which the paresis has taken a rapid course, demonstration of the condition based on anatomic examination findings is much more complicated. The so-called chronically inflammatory, ie, reparatory, processes cannot be detected with any degree of certainty or at least not with the methods of investigation used thus far, as only the degenerative and atrophic alterations become clearly apparent when these methods are applied. In the same way, the finer alterations in the ganglion cells and the nerve fibers can be detected only incompletely with the aids available; only the advanced degeneration and degenerative alterations of the ganglion cells and the wasting of the coarser nerve myelinated fibers can be distinguished, while so far the incipient affliction of the nerve cell, the function of which can be profoundly impaired even at such an early stage, and the involvement of the finer nerve plexus, which doubtless has a high functional importance, remain completely undisclosed.

We shall not come any closer to an answer to the first problem until the cell studies introduced by Nissl have been further refined; at the same time, we may hope that Golgi's method can be adapted for use in research on paresis. Nonetheless, the very important question of the involvement of the ectodermal components of the glial tissue in the pathologic process must also be freshly investigated as soon as the details of Weigert's method of glia staining are made known.

Up to the present, we are not in a position to say any more than that following death at an advanced stage or in the terminal stage of the disease after a chronic course, histologic examination discloses easily recognizable alterations of the cerebral cortex. These, however, are of relatively little importance in the differential diagnosis, because, as you know, precisely in these cases the diagnosis can easily be made based on the postmortem macroscopic findings.

In cases with what might be referred to as a rapid course, that is, when the entire duration of the illness is compressed into a few months, histologic examination yields highly characteristic, easily recognizable pictures if the so-called inflammatory phenomena have developed early or if extensive degenerative processes of the vessels (mostly of the nature of hyaline degeneration) are present. In the latter case, we find numerous massive accumulations of red blood corpuscles or blood pigment bodies in the intravascular and extravascular lymph spaces, so that it is also permissible to refer to a hemorrhagic form of paralysis. [*Editor's note: The second part of the three-part article, "Continuation," follows.*]

I will follow this critical review of the anatomic alterations in progressive paresis with a brief description of the postmortem findings that can be observed in two pathologic forms that are reminiscent of the clinical manifestations of paresis. First, I should like to draw attention to a relatively small group of cases (in the last 11 years, that is, since I became aware of this pathologic form, only eight such instances have come to my attention), in each of which a closer examination was necessary later in the course of the differential diagnosis. In this group, we find pronounced atrophy of the white matter, either confined to one or more gyri of the brain or in several sections of the hemisphere at the same time, varying only in intensity. In the most severe cases, the entire white matter of a cerebral lobe appears to have completely wasted away, so that the opposing gyri with the thread of medulla are touching each other, for example, in the region of the insula, or are only bound on the inside by the thickened ependyma of the enormously expanded ventricular segments. These alterations are seen most clearly in the occipital and temporal lobes, so that the lower and posterior horns of the ventricles are transformed to wide cavities with blind endings, while the anterior segment of the lateral ventricle is expanded relatively little and the white matter in the frontal lobe is almost uninvolved in the disease process. Even the fact that the main seat of the illness is in the posterior segments of the brain is a way to discriminate these cases from progressive paresis. The clinical manifestations and the course of illness are also characterized by features that allow a reliable differentiation from paresis. It will be best to refer to this form of illness as *encephalitis subcorticalis chronica progressiva* (the term *encephalitis* is used here, as by Thoma, in the wider sense of brain disease and not to mean inflammation of the brain) [*editor's note: translator's emphasis*].

On macroscopic examination, the cortex shows no essential changes, except for slight thinning. Granular ependymitis was seen in only four cases. The disease process begins in some cases during the same period in life as paresis also appears, ie, in the second half of the fifth decade. There is no doubt, however, that it begins far more frequently in persons on the threshold of old age, in the early 50s. In all these cases, there is pronounced atheromatosis of the cerebral arteries. It is very easy to assume that the subcortical wasting of the nerve fibers is caused by the nutritional impairments caused in turn by the arteriosclerosis. In more advanced old age, too, we find this wasting of the white matter restricted to isolated parts of the brain in cases of severe senile dementia, as I have been able to assure myself only recently. A postmortem examination was performed following the death of a 74-year-old man who had been very highly gifted intellectually and had performed his very responsible work until 2 years before, when he died of rapidly progressing mental deterioration characterized by paraphasic features. Pathologically, high-grade wasting of the white matter was found throughout the region of the occipital and temporal lobes; as a result, the posterior and inferior horns were drastically expanded and the ependyma of both were grossly thickened.

There is another group of cases closely related to the arteriosclerotic process, which I classify under the general name of "arteriosclerotic brain degeneration." As this can lead to confusion with paresis in both its anatomic and clinical aspects, I feel justified in presenting it herein. At this point, I only want to attempt a brief review of its characteristic anatomic features, leaving the clinical characteristics until later in this report.

On postmortem examination of the body organs, we find extensive arteriosclerotic processes on the great vascular trunks, on the coronary arteries of the heart, and on the renal vessels, with atrophy of the renal parenchyma. The myocardium is heavily atrophied and subject to fatty degeneration. The great vessels in the brain usually show pronounced arteriosclerotic alterations, although cases are encountered in which these changes are sharply pronounced in the body arteries, while the internal carotid artery and the basilar artery, like the main branches of these vessels, are affected only relatively slightly. The brain is mostly markedly edematous; it shows a substantial weight reduction and is poorly supplied with blood. The vascular lumina are generally markedly expanded. In the immediate vicinity of the vessels, the brain substance can be seen macroscopically to be discolored, appearing light gray to reddish brown, and slightly depressed at many points of the cortex and the white matter. In the areas of the basal ganglia and the inner capsule, in particular, there is a definite cribriform state. The cortex is pale gray, indistinct, and not very thinned; the layering is unclear; the hemispheric white matter is a dirty white and grayish white in parts; and the large bundles of fibers in the inner capsule and the brain stem show this dirty gray discoloration most clearly. The brain ventricles are markedly expanded; granular ependymitis is occasionally found in the fourth and in the lateral ventricles.

Microscopic examination of the fresh brain discloses extensive degenerative processes—simple atrophic degeneration or fatty degeneration—on the small arterial and venous vessels in both the cortex and medulla, in some cases, and (in the larger arteries) pronounced partial thickening of the inner and middle vascular membranes, the nuclei of which are distinctly increased, in other cases. The lumen is correspondingly narrowed. At many points in the vascular sheath, there is an abundance of amorphous, scaly, and crystalline blood pigment as well as many lymphoid and epithelial elements. In the immediate vicinity of the vessels, too, we find blood residues as well as granular detritus, granular balls (some of them containing pigment), myelin scales, corpora amylacea, and (in the cortex) nerve cells and glial cells in the process of disintegration. Examination of the cortex of a hardened brain shows that the myelinated nerve fibers, both those in the superficial zonal layer and those in the medullary lamina and in the radial bundles, are distinctly reduced in number. (Precisely these cases lend themselves to examination by Marchi's method to determine the extent of the degenerative process and which nerve fibers are subject to the destructive process.) Degenerative atrophic processes can also easily be detected on the nerve cells in the cerebral cortex.

Herein you have a rough outline of the picture of the degeneration of the cerebral substance caused by vascular disease. We must now ask to what extent arteriosclerotic brain degeneration can be confused with general paresis. It must first be stressed that the presence of extensive arteriosclerotic changes of the arteries in the body and/or in the brain can also be observed in cases of typical paresis. The autopsy findings referred to above include those recorded in 22 cases in which severe generalized atheroma was present. These cases include eight in which the 40th year of life had not been reached (two patients had not yet reached the age of 31 years at the time of death). There were nine cases in which death had occurred between the ages of 40 and 45 years, three in which death occurred between the ages of 46 and 50 years, and two in which death occurred between the ages of 50 and 55 years. We can conclude from this that atheromatosis is not only a relatively frequent concomitant condition (a cause?) of the paretic disease process but it also occurs in more youthful paretics in whom senile involution cannot yet play any role in the process.

It will not be a mistake in these cases if we assume a causal connection between the premature development of arteriosclerosis and the syphilitic infection in the case history. As can be seen from my observations, arteriosclerosis is encountered both as an autopsy finding in typical paresis and in arteriosclerotic degeneration. Furthermore, as the macroscopic autopsy findings can be very similar in the two conditions, it will not always be possible for us to make the differential diagnosis based on the anatomic examination findings with an adequate degree of certainty. Nonetheless, it will presumably be possible to assign the patients with progressive intellectual deterioration who do not become ill until their late 40s or early 50s and who are characterized anatomically by the criteria of minute necrotic foci of the cerebral substance around the arteriosclerotic vessels or of miliary apoplexies to the group classifiable under arteriosclerotic brain deterioration and to distinguish them from those patients with paresis. If the clinical picture just described is also accompanied by rather large hemorrhagic foci, it is even easier to distinguish it from paresis.

The clinical picture discussed later in this report is of more decisive importance. So many of its features deviate from those of typical progressive paresis that making arteriosclerotic brain degeneration into a main classification heading in its own right is probably justified.

The second procedure that can be followed to discriminate paresis from diseases with similar manifestations is via the causative explanation for the nomenclature used for these conditions. It is probably no longer contested that the paretic disease process has to be regarded as the sequela of a functional overexertion of the central nervous system, particularly of the cerebral cortex. The threshold at which the average performance capacity of an individual is exceeded is obviously extremely variable. Very different factors are involved in the precipitation of organic brain disease against the background of functional overexertion.

The first factor to be considered, as all the more recent studies have shown, is syphilis. We shall have to assume that pathologic products of the syphilitic poison exert chemical effects that bring about changes in the substance of the nerves. Whether this chemical alteration alone can lead to the extensive degenerative changes in the nerve fibers and nerve cells that characterize the paretic disease process or whether it damages the affected tissue only insofar as it makes the nerve substance less resistant to other noxious influences acting on it must be regarded as an unanswered question. I lean toward the latter view and still believe that the syphilitic infection must be followed by other noxious influences if paresis is to develop. With this interpretation, we shall be able to regard syphilis only as an indirect disease agent when the whole is considered from the aspect of origin.

Accordingly, in doubtful cases in which the diagnosis of paresis cannot be made with certainty from the clinical symptoms, it cannot be concluded, based on a note of earlier syphilitic infection in the case history, that the question of the diagnosis is resolved in favor of paresis. For it is precisely the functional and organic brain diseases whose symptoms resemble paresis that not infrequently develop in individuals who have also suffered generalized or localized tissue damage as the result of an earlier syphilitic infection. Syphilitic neurasthenia with syphilitic hypochondria, for example, is a very common clinical picture. The arteriosclerotic disease process has also arisen against the background of syphilitic infection in some cases, and the discrimination of arteriosclerotic disease of the central nervous system from the paretic disease process is by no means made easier by this consideration of the cause.

The same problem—perhaps in an even more pronounced form—is encountered in the discrimination of paresis from cerebral syphilis in the strict sense of the term. In the separation of these two pathologic conditions, the method to determine the cause can only gain a hold if syphilis is definitely present, insofar as we must strive to differentiate the specific, ie, gummous, processes more precisely from the sequelae of syphilis, the indirect tissue damage of a nonspecific nature. Viewed theoretically, the task appears to be rather easy: all diseases of the central nervous system, and specifically of the brain, that directly follow the syphilitic infection are to be assigned to the specific processes, while all late forms, ie, all diseases of the central nervous system that lag behind the specific syphilitic manifestations, so to speak, belong to the group of illnesses that are brought about indirectly by syphilis (tabes and paresis). In practice, however, everything turns out quite differently: on the one hand, it is shown beyond all doubt by clinical and anatomic examination that simultaneously with the most varied syphilitic eruptions (diseased states of skin, mucous membranes, and bones) the postsyphilitic degenerative process can also start to develop. To remain with paresis, enough cases have been reported in which the entire course of the illness has only taken 2 to 3 years from the syphilitic infection to the fatal outcome and in which specific manifestations of illness have been present in an unremitting sequence, in parallel with severe and very pronounced brain symptoms. The anatomic examination then discloses the characteristic features of progressive paresis, while consideration of the origin suggested that a specific disease process was much more probable. In cases with such a fulminant course, then, the diagnosis cannot be made with certainty from the clinical course of the illness. Conversely, we encounter patients with quite pronounced cerebral syphilis in whom the syphilis had existed for years without any obvious manifestations of disorders before the onset of a new episode of the illness.

We see, then, that consideration of the temporal sequence of the manifestations of the illness is not of much help in the differential diagnosis between cerebral syphilis and progressive paralysis, even after establishment of the common causative factor.

Discussions of the other causes of progressive paresis will not yield success in finding a crucial feature, either among the predisposing moments or among those directly involved in the causation of the illness, that can be regarded as the determining factor allowing the diagnosis to be made in doubtful cases. Heritability, which, contrary to earlier assumptions, plays an important role in paralysis, alcoholism, and the plurality of noxious influences common to all persons in civilized societies, owing to present-day social circumstances, to the existentially harder struggle, and to the exaggeratedly hasty way of life, do not cause exclusively one or the other functional or organic psychic illness. On the contrary, we have to say that the same causative factors can most certainly lead to different kinds of disease processes, depending on the predisposition and the constitution of the person affected.

The present status of our knowledge of causative relationships allows no other assumption but that in the area of neurologic diseases, the localization and extent of a disease process will be determined primarily by the degree of anatomic and physiologic development of some segment of the nervous system in the determination of the level of resistance that precisely this segment possesses against pathologic influences. Compared with this level of anatomic and functional development determined by predisposition and "training," the specific localized mechanism of action of particular noxious influences can be assumed to play a less important role.

I should like to include just one example at this point to illustrate these reflections, which I have advisedly kept on a general plane. An irregular, dissolute way of life that is also overburdened by physical or intellectual work leads in one case (with or without syphilitic infection or chronic alcohol abuse) to the typical clinical picture of organic attrition of the central nervous system, that is, to paresis. In another case, the only consequence is functional attrition with an impaired equilibrium, that is, neurasthenia. In a third case, the influence of these noxious influences [*editor's note: original word used was "noxae"*] makes itself felt primarily in organic disease of the vascular system, in those endarteritic and mesarteritic disease processes that are the cause of far-reaching functional impairments and anatomic alterations in a very wide variety of organs. Here, we see that, while the nature of the noxious influences is the same, it is the particular anatomic and functional constitution of the individual organ systems that determines the particular location and extent of the disease processes.

Here I begin the third part of my discussion, in which it is my intention to discuss the differential diagnostic aspects offered by the clinical course. I should need to speak at unreasonable length if I were to present the entire, exceptionally varied psychic and somatic signs and symptoms of paresis at this point, with reference to the value I assign to them for the process of diagnosis. It is made easier for me to evade this task, insofar as I am addressing a gathering of fellow specialists who are familiar with these clinical facts. I can therefore restrict myself to drawing attention to the mistakes that can be made in diagnosis: on the one hand, those that easily come up in the early stages of paresis, and on the other hand, those that can be made in the group of so-called atypical cases of paresis as a consequence of confusion with clinically related organic brain diseases. I shall begin with the form of illness that I have referred to earlier, in the section dealing with anatomy, as arteriosclerotic brain degeneration.

However uniform and unequivocal the anatomic findings may be, the clinical picture can vary extremely widely both in the intensity of the manifestations of illness and in the sequence of their appearance. I want now to attempt to divide these different types of clinical pictures into two groups. It will be best if I append the description of the first to the report of a case that was the subject of some controversy over whether it should be classified as progressive paresis, even among physicians qualified in our speciality.

The patient was a man in his early 50s who was physically inadequately developed with a delicate bone structure and underdeveloped muscles, soft, flabby adipose tissue, and slack skin. Those arteries that could be palpated were markedly twisted and rigid, the action of the heart was weak and arrhythmic, and the urine was increased in volume and contained traces of protein.

Intellectually, the following findings were observed: a loss of intellectual freshness and liveliness, progressing slowly, almost imperceptibly, in the course of the preceding years; temporarily, in individual situations, no loss of judgment or consistency in carrying out a plan once it was decided, although he had previously been highly developed intellectually and perspicacious. However, these times of high performance were followed by periods of extreme physical and intellectual sluggishness varying in duration, with apathetic, intellectually sluggish behavior and a pathologic tendency to sleep and with a sharply distinct lack of capacity for any intellectual effort. His judgment became blurred, his memory was impaired, in some areas severely, and the patient was weak willed, indecisive, and, at these times, ethically wanting. His mental impulses were confined to the satisfaction of base, sensual needs, which refer to culinary or sexual pleasures. Most aesthetic and ethical judgment left the patient during the satisfaction of these wishes; he was extravagant, cynical, lascivious, emotionally labile, and abnormally excitable emotionally.

The periods of capability became increasingly shorter and were gradually restricted to only a few hours of the day, eventually ceasing altogether. However, even in later stages of the course of the illness, an unanticipated, almost lightning flash of his earlier intellectual powers would be observed—to everyone's amazement—showing that while the energy needed for intellectual performance was severely impaired, the individual elements of the earlier intellectual assets were not completely lost and could on occasion be brought together to provide a continuous train of thought.

The course of the illness was also characterized by attacks of giddiness, momentary episodes of unconsciousness, lengthy periods of clouded consciousness, incoherence, loss of orientation, hallucinatory agitation, and passing manifestations of paralysis affecting isolated segments of the body musculature (eg, impaired ability to swallow and to speak, hemiparesis, and monoparesis). The patient's strength was progressively lost; the fatal outcome was precipitated by an intercurrent illness (pneumonia). [*Editor's note: The third part of the article, "Continuation, Conclusion."*]

In the above sketch of the course of illness, I have taken, as a basis, a case that ended in death within 2 years as a result of episodes of illness following each other in quick succession. An essential point I should like to stress is that despite this rapid progression of intellectual wasting, the intermittent course of the condition was unmistakable up to the last months of the patient's life and as a result of these—later admittedly short-term—remissions, the signs of intellectual loss seemed substantially less pronounced than suggested by his behavior the rest of the time. We can conclude from this that during the course of the illness, numerous processes of fatigue and inhibition (fluctuations in brain pressure, manifestations of compression, and passing nutritional disturbances) supplemented the manifestations of deficiency. If these sometimes temporarily disappear, the differential diagnosis against progressive paresis is ensured. The latter, as is known, also involves remission periods varying in duration. They do not, however, start so suddenly and unexpectedly as in arteriosclerotic brain degeneration. Rather, they represent a longer or shorter stagnation of the disease, during which a relative recovery of the intellect proceeds only slowly, and, even at the most pronounced point of the remission, the impairment of intellectual performance conditioned by the previous episode of illness remains clearly recognizable as an irremediable defect. The patients, I suppose, gradually learn to live with their remaining intellectual abilities and are capable of simple thought processes; the permanent losses, nonetheless, exclude the possibility to accomplish complicated intellectual performances comparable with those of the time when they were still in good health.

This difference between the two illnesses is very probably conditioned by the different natures of the anatomic processes in each: general paresis has a diffuse onset and, at least in the cases with a chronic course, is primarily an atrophic degenerative type of brain disease, which does not lead to signs of illness in the area of intellect until a large number of the finest associative connections have already been irrevocably lost. Arteriosclerotic brain degeneration, in contrast, starts in a focal way and most probably leads to only circumscribed areas of degeneration of the different types of fiber systems of the cerebrum.

Those cases of illness that belong, judging by their clinical course, to the second group, show the following characteristic features: the onset of illness is the same as in the first group, but the course of the illness is far more protracted, as there are remissions lasting for some months or even years between the individual episodes of illness, which are entirely similar in type to those encountered in the first group.

The patients then exhibit a clinical picture that includes abundant traits related to both postapoplectic dementia and dementia paralytica. It is characteristic for these stages of relative stagnation of the disease that the intellectual abilities are reduced. Of course, this appears in quite different ways, depending on the point at which such a resting phase happens to be observed. Quite a different stock of intellectual assets will be found in such a patient if he is examined in the early stages than if an intelligence test of this kind is performed after a long disease duration with numerous episodes of illness. In general, it is possible to say that in these cases with a protracted course, in which the individual acute and subacute episodes of illness can be far apart, the manifestations of the losses sustained are much more obvious than in the first group.

It is primarily the memory that is impaired, in a way analogous to that with which we are familiar from other acquired states of mental weakness. Facts from the past, before the onset of the disease process, can be recalled relatively well, although closer examination can disclose all sorts of gaps and errors even in memories from this period. The capacity for remembering figures and names is particularly badly compromised. The memory defect is far more obvious in its bearing on the immediate past. Even important events have been erased from the memory after a few days.

In later stages, the patients are operating in the present as though they were persons for whom there are only new and unaccustomed experiences every day. They therefore find it difficult to manage in these constantly changing living conditions. Because the patients' attention, that is, the ability to absorb and retain sensory impressions, is also profoundly impaired, their efforts are frequently in vain. The patients are disorientated and confused about their surroundings, identifying places and persons with others remembered from the time before they were ill.

The patients' weak judgment is very obvious once many memories are lost and the associative links between the remaining ones are deeply impaired. This weakness varies, of course, with the degree of impairment suffered by the aforementioned components of intellectual performance.

In many cases, a credulous or light-hearted attitude toward important decisions, presenting a gross contrast to an earlier keen judgment, is the first obvious sign of the intellectual defect, when a remission period occurs early in the disease after only a few episodes of illness. The mental impoverishment in the area of judgmental associations is much more pronounced in the later stages. Any business arrangements are completely obscure and nonsensical and fortunately are nipped in the bud, because it would be impossible to implement them. However, even the less responsible, ordinary arrangements that have to be made in everyday life are seriously affected. The patients are untidy, negligent, and indifferent to the laws of decency and propriety. The mental impoverishment ultimately leads to the complete absence of thought and judgment, typified outwardly by apathetic brooding. Any oral utterance is restricted to repetition of isolated, completely unconnected words.

The patients' mood in the later stages is generally dull and indifferent, as the sensory and intellectual nuances of feeling have been destroyed for the most part, in keeping with the general disintegration of the intellect. In the earlier stages, in contrast, pathologic accentuations of affect are almost a regular part of the clinical picture. Cheerful, angry, and anxious affect occur in any order, in a similar way to that seen in paresis. However, the euphoria typically seen in paresis is absent, particularly in the initial stages. Even in the later course, however, the patients very frequently still have a good insight into their illness and accordingly have a mournful, occasionally even despairing mood that is quite in keeping with the patients' awareness of the illness.

The many points of contact with the course of paresis with dementia are unmistakable, but the physical symptoms will make it considerably easier to draw a distinction. It is true that the motor impairment is the same in many points in the two conditions: central paralysis of the facial nerve, of the hypoglossal nerve, and of the musculature of the trunk and extremities is also a part of the clinical picture of arteriosclerotic brain degeneration. In the earlier stages, these are mainly monoparetic and hemiparetic manifestations, while later a general enfeeblement of corticomotor performance is present, admittedly with impairments on one side of the body predominating. During voluntary movements, there is usually an intention tremor—more or less pronounced—and ataxias are also observed, particularly following episodes of illness.

In contrast, in the unmixed cases, the pupillary reaction is not impaired, and the paralysis of the outer ocular muscles or the speech disturbance that are characteristic of paresis are not present. Speech becomes slow and more awkward and clumsy, but the hesitation, stumbling over syllables, slurring, and transposition of individual consonants or syllables are lacking. Aphasias can also be observed intermittently, again in the course of or subsequent to the paroxysmal processes of the disease. A closer analysis of these reveals that they are motor and sensory disturbances, but mostly so-called transcortical (paraphasic) aphasic disturbances. Optic aphasia (word blindness) is also intermittently observed.

The course of the illness in these cases is occasionally also characterized by the manifestations of a pronounced apoplectic insult, with lasting symptoms of motor deficiency on one side of the body during an episode of the illness. In this case, a superficial consideration will hardly allow discrimination of the condition from the secondary demented states following focal illness of the brain. Closer inspection, particularly consideration of the overall development, will then make the diagnosis of arteriosclerotic brain degeneration possible.

In fact, however, it should not be denied that from the aspect of pathogenesis, the focal illnesses based on arteriosclerosis (hemorrhages, embolic, and thrombotic softening) have equal weight with the form of illness described herein as generalized arteriosclerotic brain degeneration. The anatomic and clinical differences stem from the multiple or even miliary character of the foci of softening and the extensive degeneration of the cortex and white matter linked to this process. This association also explains why mixed forms are quite common, as the miliary foci are joined by larger ones with stable manifestations of deficiency.

Because this arteriosclerotic degeneration almost always begins on the borderline between the prime of life and the onset of senile involution (in the early 50s), its discrimination from simple senile dementia is also problematic, especially in the early stages. Arteriosclerotic degeneration can be differentiated by the initially relatively fast progress of the disease and the intermittent course from conventional senile dementia. I am convinced that the majority of the controversial cases in which the diagnosis oscillates between paresis and so-called premature senility [*editor's note: original term used was "senium praecox"*] belong in this category.

I should like to stress again that the arteriosclerotic disease of the kidney that is frequently present can be an important factor in determining the diagnosis. It is therefore essential to insist on a investigation. The full, hard, tense nature of the pulse will also help to ensure the diagnosis. Pronounced hypertrophy of the heart is not always present, even when kidney disease exists; the reason for this mostly has to do with the brown atrophy and fatty degeneration of the myocardium that are detectable on autopsy.

During the same period of life, we encounter cases of pronounced mental disintegration that cannot be classified as paresis in either anatomic or clinical terms. I should like to classify cases of this kind under the heading "simple presenile dementia."

This condition usually affects persons in whom intellectual development has remained at a relatively low level. While such people cannot be described as feeble minded in the usual sense of the term, such individuals do show a certain imperfection in mental development, which is characterized by an inability to see tasks through to their completion, so that they fail financially, and in some cases morally, at every turn and by the fact that these people are prematurely defeated among the everlasting toil and trouble of existence. Often, such people are only in their late 40s or early 50s when their keenness of judgment—which is hardly exceptional anyway—is restricted further, to such an extent that it is obvious even to someone who is not particularly close. Their creative ability wanes. The man who was always restless and busy becomes apathetic, weak willed, and rather indifferent; considerable gaps in memory become obvious; the posture is slack; the speech is monotonous and tremulous; and the movements of the extremities are limp and accompanied by a slight static and ataxic tremor. Some gross commercial failure—for example, the inability to continue keeping accounts, obvious errors in the administration of the petty cash, or nonsensical, pointless orders—leads to a storm and compels these persons to renounce even the last remnants of apparent work. Easy mechanical occupations or, in the case of educated persons, the study of books and periodicals, but above all their anxiety over food and drink, fill up their day. They need constant supervision, because in their pathologic overestimation of their own abilities, especially under the influence of slight emotional excitement, they independently act in an inexpedient manner or, because of their severely weak judgment and will, can be led into dangerous and even illegal actions by other people.

What these patients have in common with those affected by paresis is mental disintegration with the loss of finer aesthetic and ethical ideas. At the peak of the illness, they overlap with the clinical picture of simple paretic dementia. Nonetheless, they differ from full-blown paresis in that the typical somatic signs of illness are absent; the pupillary reaction may be rather more sluggish, but I have never observed an actually nonreactive pupil in such cases of presenile dementia. The speech is tremulous and often rather nasal and less clear; the typical hesitation or falling over syllables is absent in these cases. The facial area is weakly innervated, but there are no clearly defined signs of paralysis, such as those that are peculiar to fully developed paresis. The knee phenomena [*editor's note: patellar tendon reflexes*] are always overactive. The further course also differentiates these patients from those with typical paresis, as the progressive character is hardly pronounced; the patients remain in this same state of mental dullness and physical weakness for many years, until some intercurrent illness finally brings about death. It is not rare for such patients to die of internal hemorrhagic pachymeningitis of acute or subacute onset.

There is one causative, clinical aspect that is of decisive importance for the differential diagnosis and that can easily be established by a careful elicitation of the history. In these cases, varying degrees of inhibition of development are encountered in the intellectual sector. The action of a particular noxious influence, such as intellectual overexertion, alcoholism, and syphilis, is by no means necessary for this mentally defective state to come about; such noxious influences [*editor's note: "noxae"*], however, would presumably exacerbate the central nervous system's lack of resistance and accelerate the onset of the intellectual degeneration.

Mixed forms are encountered here as well, as true manifestations of paretic illness may be added to the clinical picture described above. In such cases, we find changes brought about by the paresis on anatomic examination, while in unadulterated presenile dementia, examination reveals only the anatomic features of the elderly brain.

An additional task still awaiting a solution is the discrimination of the cases characterized above, based on their anatomic features, as chronic progressive subcortical encephalitis, from progressive paralysis. I want to illustrate this, too, with a case report.

A factory owner in his late 40s, who had been infected with syphilis 26 years earlier, became ill after suffering from long-standing sciatic pain 12 years before and after also experiencing ptyalism, reduced sight in the right eye (disseminated choroiditis), giddiness that had begun some years earlier, severe left-sided headache, paresthesias (tingling, feelings of "pins and needles," and numbness) in the right arm and right leg, and impairment of the finer coordinated movements of the right hand and fingers, which became manifest in uncertainty, clumsiness, and more rapid fatigability during writing and dressing and undressing. No reduced perception of touch or pain was detectable objectively in the affected extremities, nor did the patient's perceptions of pressure, position, or touch show any obvious attenuation. The coarse motor strength on the right side was also unimpaired. In addition, the patient complained of difficulty with his speech, specifically that he was often unable to express his thoughts precisely because the words escaped him. He often had to have recourse to circumlocutions, because the most appropriate word did not come to mind. No difficulty with articulation or paralytic speech impairment was present. At the same time, there were sleeplessness; an unhappy, hypochondriacal mood; and fear of becoming mentally ill. It was particularly distressing for him that sometimes when he was in the middle of a conversation not only would words fail him but his memory would break down completely. When he was relating his experiences in the German-French war, for example, he would suddenly have no memory of where he had been on a given occasion or of what he had done and seen. He was able to give a good, coherent account of anything he had just experienced and of his own circumstances and those of his family, and he was fully conscious of his condition. It was striking that he found arithmetic calculations involving numbers with several digits difficult. Antisyphilitic treatments brought about a relative recovery—the headaches disappeared, as did the disturbances in the extremities, and the aphasic speech impairment diminished in severity, so that the patient's speech failed briefly only in times of physical and mental fatigue. He went about his business as before, but he did not have his earlier mental freshness; not only did he tire more quickly, but his work was also inferior in quality, as his brother and business partner were soon able to observe. The aphasic disturbances had not been substantially influenced by the antisyphilitic treatment. The reduction in intellectual capacity became more severe during subsequent years. The patient became more forgetful, especially as far as the immediate past was concerned. His judgment in business decisions dwindled increasingly, while the speech impairment progressed and became distinctly paraphasic. His affect had become characterized by easy excitability with tendencies toward fits of anger and anxious, tearful agitation. When he was 53 years of age, he had to be admitted to an institution, as he had started to have more violent fits of agitation. The patient would get up during the night to look for burglars, would talk excitedly, and, in an incomprehensible and disconnected manner, would attempt to run into the street and, if prevented from carrying out his intentions, fly into a passionate rage.

The following findings were recorded on admission on February 22, 1889, and in the later case history: scar on the right tonsil and left palatal velum; scar to the left of the frenulum preputii; no swollen glands; slight periosteal deposits on both tibiae; markedly winding arteries that were more rigid on the right side than on the left side; a pulse of 94 beats per minute; weak, pure heart sounds; normal cardiac dullness; and urinary acid that was free of protein. Pupils were average in width and were equal, and all pupillary reactions were perfectly prompt; eye movements were unrestricted; ocular fissures were equal; the left side of face and mouth were perceptibly more heavily innervated than the right side, which was obvious at rest, during activity, and in the adoption of facial expression; irregular blowing out of the cheeks—sometimes more pronounced on the right, sometimes on the left; obvious deviation of the tongue to the left side when protruded, and the tongue could also be easily protruded from the corner of the mouth; no tremor; motor strength in the upper extremities that was only slightly reduced on both sides; hand grip measured with a dynamometer on the right (75, 77, 95, 100, and 86) and left (55, 80, 78, 70, and 80); very fine manual tremor; finer arm and hand movements, such as buttoning and unbuttoning, well maintained on both sides; motor strength in lower extremities reduced on both sides, decidedly more severely on right than on left; normal gait; and absent Romberg's sign.

The patient's speech was completely disconnected and incomprehensible. He would string words together in an absolutely meaningless way. When he was shown a spoon, he called it a "school," then shook his head, obviously trying to find the right word. When "spoon" was said to him, he agreed at once and murmured the word spoon several times. The ability to repeat proved to be intact, and verbal comprehension was seen in easy exercises to be relatively well preserved. A series of objects was shown to the patient, and he was asked to give one of them, specified by name, to the physician. In most cases, he selected the correct object; occasionally, for example, when the word "pencil" was specified, he looked at the physician in amazement and did not point to the pencil right in front of him. During one attempt, he confused pencil and pen. When asked to show his tongue or to hold out his left or right hand, he was able to do so correctly.

Physician: "Where is my ring?" *Patient:* "My—your—ring?" (looks at his hand). *Physician:* "Point to my ring!" Patient draws a ring in the air with his finger. *Physician:* "Point to my ring on my left hand!" Patient looks at his left hand.

The patient's verbal designation of objects held up to him was variable, as seen by the following exchange: A clock is held up. "That is . . . well, I really don't know—Erfurt—in Erfurt." A hat is held up. "A hat." A ring is held up. "That's a hat too." A glove is held up.

That's a dog—shoe—paltry." An inkwell is held up. "Loaf of bread." *Physician:* "No it's not bread." *Patient:* "Nay, the blue thing . . ." (The inkwell looks blue.) A pen is held up. "Pen." A purse is held up. "That's—I don't know—200 and some. That's nice isn't it." Even when touching the purse, he does not come upon the correct word for it. A thaler (a coin) is held up. "A thaler." A one-mark piece is held up. "That's a 20—a silver penny, no, two." A cuff is held up. "Cuff" (quickly). He was not able to come up with the word for key but made the correct motion of unlocking.

When objects were put into his hand for him to examine them by touch while keeping his eyes closed, he identified them correctly and incorrectly, using paraphasic names in approximately the same proportions as on sight of them. It was obvious that his ability to identify objects from the way they feel was intact, because, while he sometimes gave identified an object incorrectly, when it was put into his other hand, he remarked correctly, "That's the same thing."

When reading, the patient skipped over words and phrases and rearranged others in such a way as to sound fantastic. For example, instead of "We should have preferred them to elect a Frenchman, one of our brothers in the faith, but they have followed their hearts and we accept this" (large print in newspaper), he read the following: "We should have had a Negro brother in the faith—it is a repulsive story—and their heart's decision up to early us." Further mistakes arose from the fact that the patient often wandered from one line to the next.

Although he was able to understand the request "Give me your left hand" correctly if he took his time, he did not comply with it. He consistently read isolated letters correctly when they were written for him. The patient was usually able to read numbers with three digits correctly, but they were displaced and confused when there were four or more.

The patient's writing ability was impaired. He often wrote down his own name spontaneously and correctly, but sometimes individual letters were omitted or inappropriate ones were inserted. From dictation, he wrote "Schnurrbart" (moustache), for example, as "Schurpaupa" and then, at the next attempt, as "Schutt . . . ," with a few completely illegible and incomprehensible letters. The patient wrote the word "Licht" (light) correctly from dictation. The ability to copy was also severely impaired. Instead of "Schnurrbart," he wrote "Nachbar Baupahrer," then "Nannhbarbobiterin,", and, finally, completely illegible signs.

Sensitivity to pain was retained consistently; sensitivity to touch could not be precisely tested. The smell of Peru balsam and NH_3 was apparently perceived on both sides. Words spoken quietly from half a yard away were heard with both the right and the left ears. On hearing the ticking of a clock while keeping his eyes closed, the patient concluded promptly, "That's a clock." No great impairment of the sense of taste could be demonstrated.

Facial expression was quite intelligent, although a little perplexed and surprised. If anyone smiled at him or put out his hand, he smiled cordially and shook the proferred hand quite politely, making a correct half-bow. Sometimes he clasped his hands together, and his face assumed a piteous expression. He rolled his eyes upward and tried to make something clear to the physician, but the paraphasia was so severe that it was impossible to understand what he wanted to say.

On February 24, 1889, the patient was very restless during the night, was out of bed a great deal, and was anxious to reach the door. The following dialogue took place the next day: *Physician:* "Who am I?" *Patient:* "You're the . . ." *Physician:* "Vicar?" *Patient:* "No." *Physician:* "Doctor?" *Patient:* "Yes."

The patient was often tearful and anxious, even during the daytime, and when asked a question, he frequently repeated some word in it, as if automatically. On February 28, 1889, he sang the melody to "Kommt ein Vogel geflogen" (without the words) right through, quickly and without any mistakes. At the end he said "I've had a lot to do with music."

On March 3, 1889, the patient showed increased restlessness. Only occasionally did he sit still for a few minutes; otherwise, he kept walking about everywhere with long strides as though looking for something. When anyone tried to stop him, he said, "Oh my God, just let me go. All the day I'm—just be so kind once again."

On March 4, 1889, the patient was quizzed with the following math problems: 3×2? *Patient:* "7.' 3×3? *Patient:* "9." 7×8? *Patient:* "3×3, $3 \times 3 = 9$."

On March 7, 1889, it was established that the patient was no longer able to play the piano. On March 12, 1889, when the patient was scolded violently, he sometimes used words correctly that he otherwise uttered in inappropriate context. On March 15, 1889, there was no constant pattern in the misuse of words. The patient very frequently used conventional phrases instead of saying what he wanted to say. When he read over what he had written down during a spell of paraphasia, he noticed his own spelling mistakes. On March 21, 1889, the patient put on his clothes in the wrong order.

On April 7, 1889, the patient sometimes went up to one of the other patients and paid a compliment. His bearing often gave the impression that he thought that he was at a social gathering. On May 1, 1889, it was noted that now and then he had a slight list to the right. On June 1, 1889, the patient was quite often noted to be very noisy during the night. On July 12, 1889, the patient probably recognized a relative correctly, judging from his facial expression, but he addressed him by the wrong name.

On March 4, 1890, the patient seemed to have recognized the physician he had previously seen during a visit. On May 1, 1890, the patient had recently started to repeat words wrongly as well. He often made automatic rubbing movements with his hands against his thighs. On July 1, 1890, the patient was no longer able to write his name correctly. On April 10, 1891, the test of verbal comprehension was administered as on admission. He read "Weimarische Zeitung" as "Zeitung—Schornische" and "Amtliche Nachrichten" as "Amtlich." The patient did not read any further. When he was asked to write from dictation, he wrote down only isolated letters correctly. In spontaneous writing, he also managed only isolated letters followed by illegible lines. When copying, he wrote only the first letter correctly and then added some inappropriate ones. The patient was frequently incontinent.

On February 18, 1892, the patient suffered an epileptic fit in the morning, with an initial cry, followed by tonic-clonic movements of short duration, and then coordinated thrashing of his arms and legs. Afterward, he slept for several hours. His temperature was 37.4°C. At 2 PM, the patient vomited; at 4:30, he soiled himself.

On February 19, 1892, the patient was restless and incontinent during the night, showed no impairment of cutaneous reflexes or tendon phenomena, reacted to symmetrical pin pricks, showed innervation of right- and left-sided muscles, showed no gross impairment of sight and hearing, and exhibited a somewhat reeling gait.

On June 7, 1892, the patient experienced a second epileptic insult, which was followed by violent agitation. The patient threw himself about the bed and thrashed. On December 6, 1892, the knee-jerk reflex could no longer be elicited. The patient had a temperature of 39.2°C in the evening, accompanied by diarrhea. On January 10, 1893, the patient appeared dull, apathetic, and very weak. On March 10, 1893, direct and indirect pupillary reactions were retained on both sides. The patient was more sluggish, exhibited divergent strabismus on the left side, had moderate knee-jerk reflexes on both sides, was sensitive to pain throughout his body, no longer complied with even simple requests, no longer was able to name objects held up to him, was able to repeat "Buch" (book) and "Hut" (hat), exhibited a pronounced weight loss, had to be fed, was completely incontinent, and had a fluctuating body temperature often noted in the evenings.

On June 3, 1893, the patient remained in the decubitus position and had a temperature of 39.3°C. His respiration had slowed and his face was very flushed. On June 6, 1893, at 9 PM, the patient died. A postmortem examination was performed on June 7, 1893, at 11 AM by Professor W. Müller.

The following information was taken from the report: Spinal cord: roots white; cervical spinal cord flat; substances of all kinds extremely pale; the posterior bundles beside the raphe pale grayish yellow. Upper thoracic spinal cord: anterior bundles white; grayish red-tinged radial striation of lateral bundles almost throughout, except for the mediolateral part; posterior bundles gray. Lower thoracic spinal cord: anterior bundles white; the right lateral bundle, more than the left, reddish gray, particularly in the posterior third; posterior bundles pale reddish gray in the anterior half, yellowish gray in the posterior half; gray matter very pale. Lumbar spinal cord: flat; anterior bundles white; reddish gray striation of lateral bundles, especially toward the gray matter; posterior bundles gray; gray matter very pale; central channel unrecognizable throughout. Soft meninges: thin, except for isolated, highly insignificant opacities of the arachnoid membrane; pronounced external hydrocephalus; frontal gyri obviously narrowed, with increasing intensity from back to front; dura basalis covered with reddish yellow spots of a gelatinous substance in the anterior and medial parts of the cerebral cavity. Brain weight: 1285 g.

Only isolated, insignificant opacities were seen in basilar arteries. The lateral chambers of the brain were very considerably expanded, especially the inferior horn; the cerebrum was pale throughout; and the gray matter was rather thin in the frontal part. The white matter of the lower parietal lobe and of the upper and lateral parts of the temporal lobe was extremely wasted, especially on the left side. Expansion of the lateral ventricle accordingly affected mainly the initial sections of the posterior and inferior horns; the ependyma was markedly thickened; and there were no signs of focal disease. (The more detailed examination of the brain by means of serial sections to determine the extent of medullary fiber wasting will be discussed later in conjunction with the discussion of other relevant cases.)

After hardening of the brain in potassium dichromate, the wasting of the white matter in these parts was particularly distinct. The posterior part of the hemisphere was considerably more severely reduced in size on the left compared with the right side. In a coronal section obtained approximately through the middle of the posterior branch of the sylvian fissure and the posterior margin of the operculum, the right half of the hemisphere had a maximum width of 8.7 cm, while the width of the left half at the same point was only 7.3 cm.

The above case history can be summarized as follows: Infection with syphilis in the mid-20s; first upsets affecting the nervous system (sciatic nerve) at 40 years of age; ptyalism for 1.5 years starting at age 44 years; disseminated choroiditis at age 48 years; first signs of brain disease also at age 48 years, with those of motor aphasia and later of paraphasia being the most pronounced; paraphasia and dysgraphia, paralexia and dyslexia; increasing loss of memory, confusion, incoherence, and overexcitement, while linguistic difficulties remain almost stable; at age 56 years, two epileptic insults; increasing intellectual deterioration; at age 57 years, final disintegration of strength and, finally, death. Postmortem examination revealed slight arteriosclerosis; diffuse disease of the spinal cord; no macroscopically recognizable syphilitic infection of the cerebral arteries; no substantial leptomeningitis; severe wasting of the white matter of the parietal and temporal lobes, especially on the left side; and moderate atrophy of the cortex of the frontal lobe.

The development and the course of the illness also suggest that the disease process must have destroyed parts of the medullary fibers in the left hemisphere, specifically the following tracts: (1) between the centers for image formation and the acoustic speech center and between these and the reading and writing centers; (2) between the reading and writing centers and the acoustic speech center; and (3) between the acoustic and the motor speech centers.

In keeping with this extensive, but functionally and anatomically only fragmentary, destruction of association fibers, the aphasic symptoms are very varied and equivocal. It includes a mixture of features that are characteristic of both transcortical and intercenter tract aphasias. At this stage, of course—before precise and thorough examination of the brain—it is quite impossible to say whether it is exclusively association and interhemispheric fibers that are destroyed or whether projection fibers are also affected. Even the macroscopic findings allow the conclusion that the latter is probably true. The speech impairment would then be attributable in part to the latter explanation, and signs of an incomplete agnostic sensory aphasia and alexia could accordingly be expected to be added to the disturbances listed above. (Herein, I make use of the terms used by Ziehen in his clear and well-structured treatment of aphasia for the individual aphasic conditions ["Aphasie," in *Real Encyclopaedie*, 3rd ed].)

We can be sure that further in the course of the illness, the wasting of the nerve fibers is not confined to the regions of the brain specified above. The final intellectual disintegration suggests that innumerable tracts in the entire medulla of the hemisphere have been damaged and ultimately destroyed on both sides of the cerebrum. The involvement of the intracortical conduction fibers can also only be established by means of precise histologic examination. As seen from the sectional investigation mentioned above, the spinal cord is also affected by the degenerative processes.

I shall have to be content with this one example here. I hope to be able to give a more detailed account of this condition eventually, based on a full and accurate description of eight relevant cases. These vary in some features; the characteristics common to all and peculiar to this condition are as follows: onset of illness on the threshold of old age (early 50s) or actually in the senium (early 60s); slow development of the deterioration of the intellectual capacities, noticeable primarily in the gradually progressing difficulty in association and ultimate loss of the associative connection between particular sensory areas in the cortex or motor segments (as in the case described above); hemiamblyopia or hemianopsia; and hemiparesis with loss of perception of pressure, position, and touch. At the peak of the illness, these symptoms of deficiency are quite stable and are associated with a generalized and unremittingly progressive reduction of intellectual ability; the patient's mental operations are later restricted to an extremely small scope. All more ambitious intellectual interests start to fade and eventually a state of severe intellectual devastation develops, in which the patient is devoid of any independent will power and either lies in bed in an apathetic, glazed manner with a completely stupefied facial expression or, if they have been washed and dressed, walk about the room without aim or purpose. If I may be allowed to make a comparison at this point, when they reach this terminal stage, the patients are like the decerebrated animals used by Goltz in his experiments.

Apoplectiform fits occur during the course of the illness, corresponding in their mildest form to attacks of giddiness and fainting and characterized in more complicated forms by unconsciousness varying in duration and by paralysis on one side of the body with corticomotor irritation (clonic twitching) in the paretic muscles and fully developed manifestations of aphasia (motor and sensory aphasia, dyslexia, optic agnosia, word blindness, etc). Full-blown epileptic fits are occasionally also seen as part of the clinical picture. Furthermore, prolonged phases of psychic agitation develop, sometimes lasting weeks or months, during which the patients show increased motor agitation (restless rushing about and loud shouting), sleeplessness, choleric irritability, complete incoherence, confusion with acceleration of the imagination, and innumerable misperceptions. The course of the illness is extremely protracted (10 years or longer) in the majority of cases. There is often a remission lasting for some years; the illness is then wrongly interpreted as a focal affliction (softening, hemorrhage, or embolism) of particular regions of the cortex with subsequent dementia, as a consequence of the localized and stable deficiencies. Death occurs during an apoplectiform fit, as a result of some intercurrent illness, or during the terminal stage of dementia as a direct result of decubitus, marasmus, and cardiac arrest.

These cases differ from paresis (1) in the stable manifestations of deficiencies; (2) by the peculiar development of the intellectual defect (patchy loss of memory, difficulties with connections, and breakage of connections between the individual corticomotor and corticosensory centers); (3) in the characteristic course (the average duration of illness is much longer than in typical paresis); and (4) in the postmortem findings.

Clinical differentiation from arteriosclerotic brain degeneration is possible based on the following: in the former condition, the focal manifestation of a transitory nature and the deficiency symptoms indicate a diffuse affliction of the brain from the very beginning, while in the latter the disease process initially has a circumscribed character confined to particular regions of the hemisphere, so that isolated deficiency syndromes of the type described dominate the clinical picture from the start. Given the close relationship between the anatomic processes, there are doubtless also intermediate forms in which the stable deficiency symptoms that are restricted to particular sensory or motor functions are less pronounced and relatively inconspicuous compared with the general intellectual defect precipitated by the generalized nerve fiber wasting and/or loss of associative connections. Postapoplectic dementia borders on this form of illness. The clinical picture differs from that of the first-named condition both in the development (the acute onset of illness with fully developed apoplectic insult) and in the course (stable character of the clinical picture with regard to both the localized manifestations of deficiency and the intellectual defect). In particular, however, the postmortem findings are quite different. It is not difficult to differentiate this postapoplectic dementia from typical paresis in the majority of cases. The development and the particular form of the intellectual defect, the manifold changes, and the peculiar association of somatic and psychic manifestations of illness, like the course, are sufficiently characteristic in general paresis to guard against such confusion.

Syphilitic focal disease, in contrast, quite often is difficult to diagnose. Pronounced focal symptoms, eg, motor aphasia, hemiparesis, and hemianopsia, varying in duration are known to occur in both disease processes, although they are completely different anatomically. Discrimination between the two is especially difficult in the initial stages, when the intellectual defect peculiar to paresis is not yet pronounced. Subsequently, it is almost impossible to differentiate paresis with an acute onset and fulminant course from the syphilitic focal disease that is associated with extensive gummous meningitic processes and has led to severe generalized signs and symptoms (prolonged spells of profound inhibition of thought or incoherence, hallucinatory agitation, etc). The differential diagnosis is more difficult, because certain somatic manifestations of response and of deficiency are characteristic of both conditions—paralysis of individual external optic muscles, oral branch of the facial nerve and the tongue, hemipareses of the extremities, and clonic twitching in the paretic muscles. If the internal ocular muscles are intact, so that the pupillary reaction is not impaired, or if only a unilateral pupillary impairment is present—with simultaneous disturbance of the reaction to light and the accommodation reaction—cerebral syphilis is more likely. It can become almost impossible to differentiate cerebral syphilis from the prodromal or initial stage of paralysis when bilateral nonreactivity of the pupils, manifestations of intellectual fatigue or exhaustion, recurrent headaches, and hypochondriacal depression are present. In such cases, a decision as to the diagnosis is only possible following most precise observation of the course of the illness and, above all, of the influence of antisyphilitic treatments. However, it must never be forgotten that, in keeping with the anatomic demonstration of the simultaneous presence of specific and postsyphilitic brain disease, the clinical features of both conditions can also occur together at an early stage, thus making discrimination impossible.

Differential diagnosis between alcoholic and paretic dementia has long concerned psychiatrists. The very term *alcoholic pseudoparesis* is an indication of the close clinical kinship of the two illnesses. The mental devastation, lack of judgment, and dulled affect can certainly have the same qualities in both. The somatic manifestations, too, are similar to those of paresis, especially in the cases of alcoholic dementia with concomitant neuritic disease affecting peripheral nerves; paralysis of the facial and hypoglossal nerves, paretic weakness of the muscles of the extremities and trunk, tremor, impaired conductivity, and suppression of the tendon reflexes provide ample opportunity for confusion. However, if the pupillary movement in response to light stimuli is not impaired, if the speech, while tremulous, is not hesitant, and if the patient is mentally dull but does not show the lack of judgment typical for those affected by paresis with respect to the entire complex of self-images, then the diagnosis will tend toward alcoholic dementia. Nonetheless, it is mostly the course of the illness that shows us whether our diagnosis is correct. Even severe forms of alcoholic dementia are amenable to cure or recovery if the noxious influence—the abuse of spirits—can be avoided, while paresis with progressive dementia never shows remissions. The somatic features of alcoholic pseudoparesis, too (tremor, paresis, loss of tendon reflexes, and impaired sensitivity), especially when precipitated by a peripheral nerve disease, can be completely reversed. In such cases, however, we must always bear in mind that the boundaries between alcoholic and paretic dementia are fluid.

Recently, cases of psychosis have been described that have occurred following acute (toxic?) [*editor's note: author's parentheses*] polyneuritis. These cases are characterized by marked psychic agitation, incoherent and agitated succession of images with loss of orientation, and poor memory for the recent past (Korsakoff). These psychic disturbances are encountered in an analogous form in cases of paresis with an acute course, so that the two conditions can be confused if the signs of polyneuritis are overlooked or cannot be observed because of high-grade mental agitation and confusion in the patient.

The only one of the different clinical varieties of paresis that needs to be mentioned separately is taboparesis. If paretic disease accompanies classic tabes that has already been present for some years, the course of the paralytic disease is often very prolonged (lasting 8 to 10 years). The intellectual deficiency progresses very slowly; even when finer aesthetic and ethical ideas and feelings are profoundly prejudiced, the patient's memory and judgment for all other mental processes may nonetheless have suffered only an extremely slight deterioration. Patients of this type become coarse, unfeeling, and choleric and lose all sense of decency in thought and action, but they are still perfectly able to carry out coherent and complicated mental operations, particularly if they were educated, intellectually highly gifted persons before their illness; for example, they are still able to perform literary work, which demands good comprehension and memory. Even severe attacks of paralysis or intercurrent spells of agitation with acute onset, often of some weeks' duration, and occasionally a completely confused state, are not characterized by such limited intellectual defects in the first and second years during which these are not at all apparent to outsiders but only the closest members of the patient's family, eg, wife and children, notice them as manifestations of ethical impoverishment and strange personality changes. The illness is often misdiagnosed at this stage because the patient still has enough self-control and thought and speech patterns are sufficiently logical and reasonable to enable the patient to deceive the physician as to the severity and implications of these ethical defects. In such cases, it is very easy for the physician to assume that he is confronted with an instance of the emotional irritability that is so frequently associated with tabes. However, a more precise intelligence test will show that there really are deficiencies in the ethical field.

The patient can no longer properly honor his obligations in this area. He is completely unaware of his tactlessness and the ethical solecisms he commits. His judgment concerning his personal affairs, particularly his material or financial assets, is also severely impaired; he is careless and wasteful. Disturbances not belonging to the conventional clinical picture of tabes can also be found in the somatic sector: paresis of the oral branch of the facial nerve and hesitation in speech are usually seen during the course of a reasonably long observation period.

The practical importance of these cases and their differentiation from simple tabes become particularly clear when the physician is approached about protection from the patient and commitment to an institution is considered. I was recently in the position of having to assess a case of this kind, in which the patient vigorously denied the existence of any mental illness and repudiated what his relatives said as slanderous. It was not possible to commit him to an institution for quite some time, as more distant relatives and the forensic medical expert denied the presence of paretic mental illness.

To conclude my remarks, I must consider the differentiation of paresis from the states of functional exhaustion that we have recently started to include under the concept of neurasthenia. In severe cases with a long course, neurasthenia passes imperceptibly into hypochondria; the exhaustion neurosis develops into an exhaustion psychosis. If we consider the cause of both, the overstretching of the nervous work output, it is easy to understand that their precise differentiation from progressive paresis can be extremely difficult, at least in the earliest phases, whether regarded from the point of view of the origin or of the clinical picture. What criteria guarantee that in one case only a functional attrition is present, with the possibility of complete recovery, while in another case with very similar symptoms the functional overuse has already led to irreversible material damage? In the so-called prodromal stages, it is completely impossible to differentiate precisely between functional symptoms of inhibition or exhaustion and lasting symptoms of intellectual loss. To make allowance for this problem, there has often been mention of a neurasthenic preliminary stage of paresis. It is impossible to make a definite diagnosis of paresis when unmistakable somatic symptoms of deficiency (paradoxal sign and nonreactive pupils) are present, while slight asymmetry of the facial innervation, slight speech disturbances (not uncommon in neurasthenics in the presence of affective agitation or against a background of hypochondriacal compulsive ideas), giddiness, and the entire multitude of subjective symptoms of illness can only be used for the differential diagnosis with caution and with due consideration for the full range of manifestations of the illness.

If objective signs of any organic disease of the brain and spinal cord are lacking, and if we have recourse mainly to the assessment of the psychic condition in establishing a diagnosis of paresis, all sorts of mistaken diagnoses are possible in addition to confusion with neurasthenia and hypochondria. As is well known, the affective and intellectual symptoms of incipient paralysis can mimic every functional psychosis. Confusion with mania and/or melancholia is the most common mistake. In the case of hallucinatory agitation, too, however, differentiation from acute hallucinatory paranoia, but especially amentia (exhaustion psychosis), is rather uncertain. In all these pictures of paresis, the psychic deficiency symptoms, the lack of judgment, the lacking ethical sense, and the memory impairment can be concealed by an imbalance of stimulatory and inhibitory processes (excessively cheerful or mournful mood, anxious affect, motor agitation, flight of ideas, hallucinations, etc). The diagnosis is confirmed as soon as the decisive feature of the illness, ie, dementia, can be observed. In this, we can always most safely be led by exploration of the assets in terms of ethical and aesthetic feelings and ideas and the quality of the judgmental associations relating to the relationship of the patient's own personality to the processes of the outside world. If defects are found in these areas, there can hardly be any further doubt that a diagnosis of paralysis is appropriate.

As this review of the discrimination of paresis from other disease states bordering on paresis shows us, there are cliffs enough against which the diagnosis can come to grief. Differentiation of the different forms of organic brain disease is predominantly of purely scientific interest. From the point of view of the prognosis, all these different types of illness affecting the central nervous system are equivalent; that is, they all ultimately lead to disintegration of the intellectual capacities. The only exception is cerebral syphilis, which is amenable to a complete cure if therapeutic intervention is instituted sufficiently early and is sufficiently vigorous. The differential diagnosis between this condition and paresis is therefore the one that has the greatest practical significance.

Discrimination of paresis from the functional neuroses and psychoses is of practically equal importance. Among colleagues, I need say no more on the subject of how ominous mistakes in this area of differential diagnosis can be, not just for the future of our patients but also for the physical and mental well being of their families.

COMMENTARY

In recent years, Binswanger's disease has become a topic of renewed interest and controversy.[1-4] Despite comprehensive reviews, a complete translation of Binswanger's original report into English is not yet readily available.[5] The present translation attempts to retain the tone of the late 19th century scholarly language, which is now rather stilted in German as in English. The German word "paralyse" has been translated as "paresis" or sometimes as "general paresis" when it clearly refers to the condition caused by syphilis, and otherwise as "paralysis." Latin terminology has generally been translated into American usage.

Binswanger's goal was to distinguish purely vascular disease of the brain from the progressive paresis that was so prevalent in his time as to dominate neuropsychiatry. In his lecture, he discussed the characteristics of progressive paresis and contrasted them with the clinical and neuropathologic findings in the two forms of vascular brain disease that he called "chronic progressive subcortical encephalitis" (now called Binswanger's disease) and "arteriosclerotic brain degeneration."

The characteristics of chronic progressive subcortical degeneration were, clinically, onset at the threshhold of old age or in the senium; a protracted course; reduction in intellectual capacities, with early impairments of associations, complex skills, and focal deficits; and later agitation, paranoia, seizures, disturbances of consciousness, and eventually a decerebrate state. The neuropathologic characteristics were atrophy of white matter, particularly in the occipital and temporal lobes, with very little involvement of the frontal white matter and only minimal cortical atrophy. The damage was particularly to association fibers. The basal and posterior horns of the ventricles were enlarged, whereas the anterior parts of the lateral ventricles were expanded only very little. The cerebral vessels showed evidence of severe atherosclerosis.

The characteristics of arteriosclerotic brain degeneration were clinically identical to those of chronic progressive subcortical degeneration, with the important exception that isolated, focal deficits dominated the clinical picture from the beginning. The clinical deficits were intermittent and included reduction in intellectual capacities, including short-term memory, perception, acquisition, and other areas of cognition. Emotional lability occurred early, and more persistent personality changes emerged as the condition progressed. Pathologically, the condition was associated with generalized as well as cerebral atherosclerosis, with atrophy or fatty degeneration of both the small arteries and veins in both the cortex and white matter. Focal lesions were prominent, as was diffuse loss of cortical neurons.

In summary, Binswanger distinguished not only between general paresis and cerebrovascular disease but between two broad forms of cerebrovascular disease: a subcortical white-matter disease and a more general condition involving both gray and white matter. In chronic progressive subcortical encephalitis, the brain tissue changes appeared to be confined to white matter only and particularly to the areas supplied by the posterior cerebral artery. In contrast, in arteriosclerotic brain degeneration, changes were evident in both gray *and* white matter and were not confined to an area supplied by a specific cerebral artery.

In 1895, Binswanger lectured further about the "Delineation of General Paresis,"[6] repeating the views he had presented in 1893. He emphasized the existence of two different vascular diseases of the brain, one affecting primarily white matter. In the discussion of this lecture,[7] Alois Alzheimer emphasized that Binswanger was the first to attempt to separate two different arteriosclerotic brain diseases from general paresis. Alzheimer himself also reported on "arteriosclerotic atrophy of the brain."[8] According to Alzheimer, the onset of disease was between ages 45 and

55 years, with men affected more often than women. Generalized atherosclerosis was typically present. Prodromes included headache, vertigo, rapid fatigue, and emotional lability. Then memory loss developed, followed by global cognitive impairments and instability of affect. Pathologically, there was generalized atherosclerosis. Relatively little atrophy of cereberal cortical or other brain structures occurred. Within the cortex, there were foci of degeneration, with small aneurysms and multiple small areas of hemorrhage and gliosis surrounding degenerating vessels. Alzheimer suggested that because of the distinct clinical symptoms, course, and neuropathologic findings, "one may have reasons enough to distinguish arteriosclerotic atrophy of the brain as a disease on its own distinct from other brain diseases."

In 1910, in his widely used textbook, Emil Kraepelin described Alzheimer's "senile brain devastation" as a consequence of senile arteriosclerosis, particularly in small vessels entering the cortex from the brain surface.[9] He proposed that these vessels occlude gradually, leading to a simple atrophy of nerve tissue.[10]

Within the last 5 years, Binswanger's disease has become a subject of renewed interest and controversy, particularly in reference to the white-matter changes evident on computed tomographic scans and magnetic resonance images.[1-4,11-19] When Binswanger wrote the article that is translated herein, the new stains recently developed by Nissl and Weigert were on the cutting edge of neuroscience research, and computerized brain imaging was unimaginable. It is therefore gratifying that Binswanger's clinical insights may still be relevant nearly 100 years later. He recognized that the clinical signs and symptoms of vascular damage to white matter, like the clinical manifestations of vascular damage to the gray matter that provide the cells of origin of the fibers in white matter, depend in large part on the location and extent of tissue damaged. He recognized that the amount of brain damage necessary to push a patient across the threshhold of clinical disability depended in part on how much brain function the patient had premorbidly and in part on how much was demanded of the patient in the way of performance. Those insights may be relevant to the clinical variability that has been associated with evidence of white-matter damage in imaging studies, including the evidence of marked radiologic abnormalities in people with no clinically important disabilities.

Binswanger's observation that vascular damage to white matter can occur with relatively little damage to gray matter is in accord with subsequent experimental studies in animals. Thus, controlled hypoxemia (arterial Po_2, 28 to 30 mm Hg) increased 2-deoxyglucose utilization in white matter in columns associated with penetrating arteries, with little effect on gray matter.[20] This relative vulnerability of white matter was attributed to a less extensive blood supply. Binswanger's observation of relatively selective damage to the white matter supplied by the posterior cerebral artery may relate to subsequent observations of anatomic differences among the cerebral arteries.[21] Among the important differences between Binswanger's time and the present is the age at onset of the senium, which Binswanger put at 60 years but which is now more often put by geriatricians in the middle or late 70s.[22]

It is hoped that the availability of this classic article to those who easily read English but not German will facilitate the continued contribution of Binswanger's original insights into the complex problems of dementing diseases, including the condition that has given him eponymic medical immortality.

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References

1. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol*. 1986;19:253-262.

2. Babikian V, Roper AH. Binswanger's disease: a review. *Stroke*. 1987;18:2-12.

3. Brust JCM. Vascular dementia is overdiagnosed. *Arch Neurol*. 1988;45:799-801.

4. Summergrad P, Peterson B. Binswanger's disease, I: the clinical recognition of subcortical arteriosclerotic encephalopathy in elderly neuropsychiatric patients. *J Geriatr Psychiatry Neurol*. 1988;2:123-133.

5. Binswanger O. Die Abgrenzung der allgemeinen progresiven Paralyse. *Berl Klin Wochenschr*. 1894;31:1103-1105, 1137-1139, 1180-1186.

6. Binswanger O. Die Begrenzung der allgemeine Paralyse. *Allg Zeitschr Psychiatr*. 1895;51:804-805.

7. Alzheimer A. Discussion. *Allg Zeitschr Psychiatr*. 1895;51:806.

8. Alzheimer A. Die arteriosklerotische Atrophie des Gehirns. *Allg Zeitschr Psychiatr*. 1895;51:809-811.

9. Kraepelin E. *Psychiatrie: Ein Lehrbuch fuer Studierende und Aertzte*. 8th ed. Leipzig, East Germany: Johann Ambrosius Barth; 1910:620-621.

10. Bick K, Amaducci L, Pepeu G, eds. *The Early Story of Alzheimer's Disease*. Padua, Italy: Liviana Press; 1987.

11. Krishman KRR, Goli V, Ellinwood EH, France RD, Blazer DG, Nemeroff CB. Leukoencephalopathy in patients diagnosed as major depressive. *Biol Psychiatry*. 1988;23:519-522.

12. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in subjects with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). *Arch Neurol*. 1987;44:32-35.

13. Inzitari D, Diaz F, Fox A, et al. Vascular risk factors and leuko-araiosis. *Arch Neurol*. 1987;44:42-47.

14. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in demented patients with diffuse white matter lucencies on computed tomographic scans (leuko-araiosis). *Arch Neurol* 1987;44:36-39.

15. Rao SM, Mittenberg W, Bernardin L, Haughton V, Leo GJ. Neuropsychological test findings in subjects with leukoaraiosis. *Arch Neurol*. 1989;46:40-44.

16. Tomanaga M, Yamanouchi H, Tonghi H, Kameyama M. Clinicopathological study of progressive subcortical vascular encephalopathy (Binswanger disease) in the elderly. *J Am Geriatr Soc*. 1982;30:524-529.

17. Lotz PR, Balinger WE, Quisling RG. Subacute arteriosclerotic encephalopathy: CT spectrum and pathologic correlation. *Am J Radiol*. 1986;147:1209-1214.

18. Coffey CE, Figiel GS, Djang WT, et al. White matter hyperintensity on magnetic resonance imaging: clinical and neuroanatomical correlates in the depressed elderly. *Neuropsychiatry Clin Neurosci*. 1989;1:135-144.

19. Libon DJ, Scanlon M, Swenson R, Coslet HB. Binswanger's disease: some neuropsychological considerations. *J Geriatr Psychiatry Neurol*. 1990;3:31-40.

20. Pulsinelli WA, Duffy TE. Local cerebral glucose metabolism during controlled hypoxemia in rats. *Science*. 1979;204:626-629.

21. Burnstock G. Ultrastructure of the vascular neuroeffector apparatus, with special regard to brain vessels. In: Owmen C, Edvinsson L, eds. *Neurogenic Control of the Brain Circulation*. New York, NY: Pergamon Press Inc; 1977:3-14.

22. Rowe JW, Kahn RL. Human aging: usual and successful. *Science*. 1987;237:143-149.

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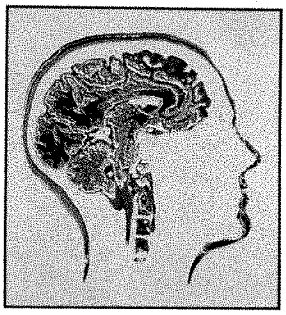

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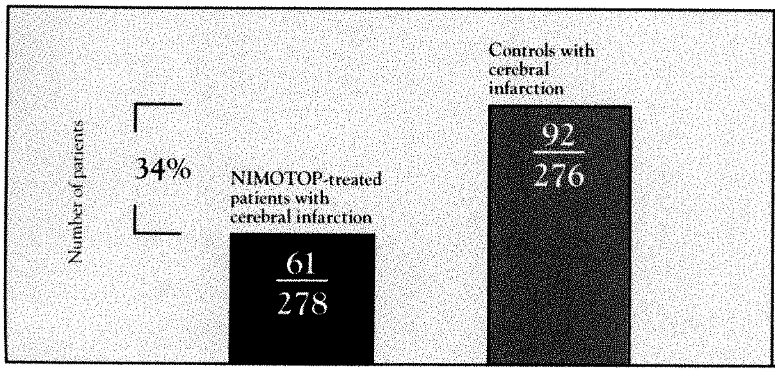
REDUCES INCIDENCE OF CEREBRAL INFARCTION IN PATIENTS FOLLOWING SUBARACHNOID HEMORRHAGE

In the largest study to date, NIMOTOP demonstrated a significant reduction in incidence of cerebral infarction[1]

- Twenty-two percent (61/278) of NIMOTOP-treated patients experienced cerebral infarction vs. 33% (92/276) of controls
- NIMOTOP reduced the incidence of cerebral infarction by 34%

Thirty-four percent reduction in incidence of cerebral infarction with NIMOTOP-treated patients vs. controls (n=554; p=0.003)[1]*



*90% of patients in this study were Hunt and Hess Grades I-III.

Dose: 60 mg (two 30 mg liquid-filled capsules) every 4 hours for 21 days commencing within 96 hours of SAH.

Adapted from Pickard, et al.[1]

NIMOTOP modulates calcium influx to promote cerebral perfusion, and may directly protect neurons[2-5]

"[In animals] The beneficial cytoprotective effect of nimodipine, probably related to normalization of calcium homeostasis and blood-brain barrier permeability after ischemia, may reflect both vascular and cellular sites of action."[6]
Lazarewicz JW, et al. *Stroke* 1989.

"[In humans] The data thus suggest that nimodipine neither prevents nor reverses cerebral vasospasm. Calcium channel blockers such as nimodipine may have an effect on cerebral arterioles that are below the limits of resolution of angiography. . . . "[1]
Pickard JD, et al. *Br Med J* 1989.

Please see references and Brief Summary of full prescribing information on next page.

MILES

CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

NIMOTOP REDUCES THE INCIDENCE OF CEREBRAL INFARCTION FOLLOWING SUBARACHNOID HEMORRHAGE

BRIEF SUMMARY
NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

MILES

Manufactured by: **Miles Inc.**
Pharmaceutical Division
400 Morgan Lane
West Haven, CT 06516

Encapsulated by: **R.P. Scherer North America**
Division of R.P. Scherer Corp.
Clearwater, FL 33518

PD100667 1/89 BAY e 9736 5202-7-A-U.S.-1 0703

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Printed in USA

REFERENCES
1. Pickard JD, Murray GD, Illingworth R, et al. *Br Med J.* 1989;298:636-642. **2.** Solomon RA, Fink ME. *Arch Neurol.* 1987;44:769-773. **3.** Petruk KC, West M, Mohr G, et al. *J Neurosurg.* 1988;68:505-517. **4.** Rodriguez R, Baena Y, Gaetani P, Grignani G, Pacchiarini L. *Acta Neurol Scand.* 1987;76:267-271. **5.** Scriabine A, van den Kerckhoff W. *Ann NY Acad Sci.* 1988;522:698-706. **6.** Lazarewicz JW, Pluta R, Salinska E, Puka M. *Stroke.* 1989;20:70-77.

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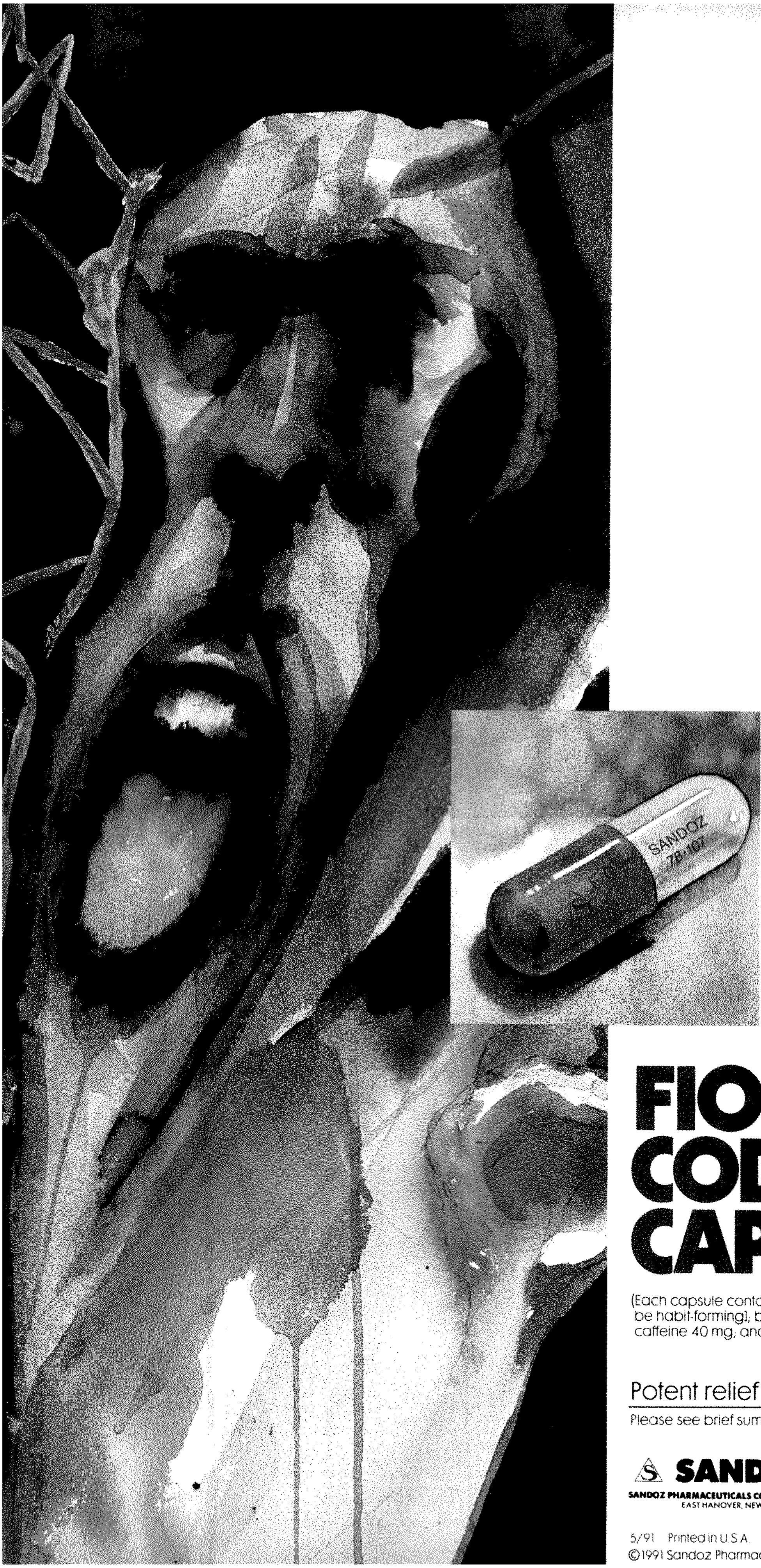

HEADACHE DESCRIBED

"Headache"– a personal interpretation of headache pain by John Crowley, a headache patient.

HEADACHE RELIEVED

Effectively treats the pain of muscle contraction headache as well as the anxiety and tension that magnify it

FIORINAL® WITH CODEINE CAPSULES Ⓒ III

(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

Please see brief summary on following page.

SANDOZ

SANDOZ PHARMACEUTICALS CORPORATION
EAST HANOVER, NEW JERSEY 07936

5/91 Printed in U.S.A. FWC-1290-01

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BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE (III CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming]; butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Placebo (N = 377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheacedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Aspirin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea; acid-base disturbances with development of metabolic acidosis; vomiting and abdominal pain; tinnitus, hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

SANDOZ PHARMACEUTICALS
Corporation, E. Hanover, NJ 07936 (201) 503-7500

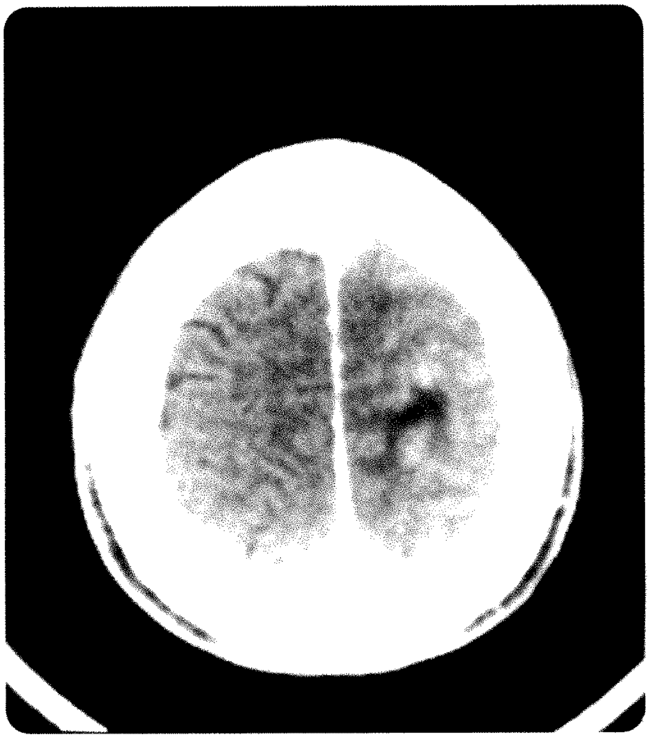
[NOVEMBER 1, 1990 FWC-Z26]

THE DECISION IS YOURS.

COMPARE.

THE CASE: A 40-year-old man presented with a 2-month history of involuntary muscle contractions of the right arm and mild weakness of the left leg.

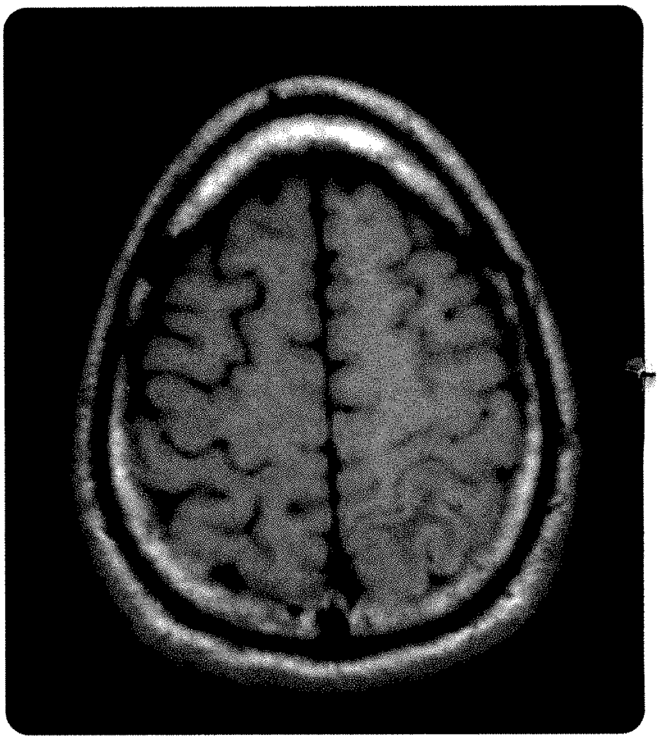
First there was CT.



Contrast CT scan shows an area of low attenuation in the left parietal lobe. A questionable focus of contrast is seen, but this may represent cerebral cortex.

Images courtesy of Michael R. Ross, MD, Stanford University Medical Center, Stanford, California

Then MRI.



T1-weighted (TR 800/TE 20) unenhanced MR image, obtained with a 1.5-T imager, shows subcortical hypointensity in the left posterior parietal lobe. The surrounding sulci appear to be compressed, but a mass is not clearly appreciated.

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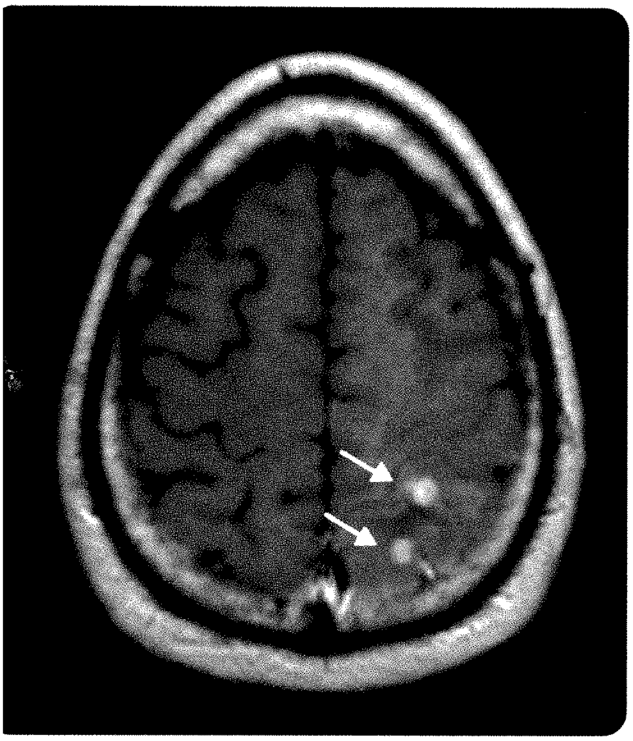
AND CONTRAST.

Now, *Magnevist*®-enhanced MRI lets you see even more.

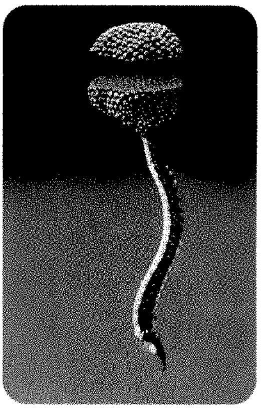


1-weighted (TR 800/TE 20) image enhanced with MAGNEVIST® injection reveals two discrete nodules arrows). This nodular enhancement is highly suggestive of a primary brain tumor, which was confirmed upon biopsy to be an astrocytoma.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

NOTHING LOCATES LESIONS BETTER

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.



Well tolerated[1] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCE: 1. Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 μg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).
Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.
Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.
Nervous System: Agitation, thirst, convulsions (including grand mal).
Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.
Skin: Rash, sweating, pruritus, urticaria (hives).
Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.
Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.
Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.
Digestive: Constipation, diarrhea.
Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.
Skin: Facial edema, erythema multiforme, epidermal necrolysis.
Special Senses: Eye pain, ear pain.
Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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N-Methyl-D-Aspartate Antagonists in the Treatment of Parkinson's Disease

J. Timothy Greenamyre, MD, PhD, Christopher F. O'Brien, MD

• Current long-term treatment of Parkinson's disease is inadequate, and improved symptomatic and neuroprotective therapies are needed. Recent interest has focused on the use of antagonists of the *N*-methyl-D-aspartate (NMDA) subtype of glutamate receptor in Parkinson's disease. Abnormally increased activity of the subthalamic nucleus is postulated to play a central pathophysiological role in the signs of Parkinson's disease, and NMDA antagonists may provide a means of decreasing this activity selectively. Like dopaminergic agonists, NMDA antagonists can reverse the akinesia and rigidity associated with monoamine depletion or neuroleptic-induced catalepsy. Very low doses of NMDA antagonists markedly potentiate the therapeutic effects of dopaminergic agonists. There is evidence that the beneficial effects of anticholinergic drugs and amantadine may be mediated, in part, by NMDA receptor blockade. Moreover, NMDA antagonists provide profound protection of dopaminergic neurons of the substantia nigra in the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and methamphetamine models of Parkinson's disease. The clinical use of NMDA antagonists may prove useful in Parkinson's disease to treat symptoms and retard disease progression.

(*Arch Neurol.* 1991;48:977-981)

Long-term treatment of Parkinson's disease is inadequate and, despite current therapies, the disease progresses. The initially gratifying response to therapy is eventually replaced by a fluctuating response to levodopa and other dopaminergic agents. Within 5 years of diagnosis, most patients receiving levodopa therapy experience fluctuations in their motor function ranging from periods of good mobility, often accompanied by dyskinesias, to periods of relative immobility.[1,2] As the disease progresses and the "therapeutic window" for dopaminergic agents narrows, motor fluctuations become less predictable and more difficult to manage. Clearly, improved therapies are needed.

The conventional strategy for therapeutic intervention is the rational development of drugs to provide more effective symptomatic relief. For a century, the only effective treatment of Parkinson's disease was anticholinergic therapy, but the mechanism by which these drugs produced a beneficial response was unknown.[3] The first rational treatment, levodopa,[4] was developed after the demonstration of a severe dopamine deficiency in Parkinson's disease.[5] Subsequent efforts at drug design have focused primarily on dopamine receptor agonists[6]; however, as the anatomical, biochemical, and pharmacological features of neurotransmitter interactions in the basal ganglia are elucidated, it is likely that drugs targeted at other transmitter systems and receptors may also prove useful clinically.

Although the ultimate cause of Parkinson's disease is not known, a second strategy for pharmacological intervention is the use of neuroprotective agents to retard neuronal damage and death. Slowing the rate of disease progression would be expected to forestall, or even prevent, the emergence of disabling motor fluctuations. This strategy was central to the DATATOP (*D*eprenyl *a*nd *T*ocopherol *A*ntioxidative *T*herapy *o*f *P*arkinsonism) study, which showed an apparent slowing of the natural course of Parkinson's disease in patients treated with deprenyl.[7] Although the DATATOP results are preliminary, the goal of developing protective therapies in Parkinson's disease is novel and important, and it needs further exploration.

A growing body of evidence suggests that modulation of the activity of the major excitatory neurotransmitter, glutamate, may be beneficial in Parkinson's disease (Table). Overactivity of the subthalamic nucleus, thought to play a crucial role in parkinsonian signs, may be reduced by glutamate receptor antagonists. In some cases, dopamine receptor agonists and glutamate receptor antagonists have similar actions at both the biochemical and behavioral levels. Additionally, the beneficial effects of "anticholinergic" drugs and amantadine may be due, in part, to their blockade of glutamate receptors. Finally, glutamate receptor antagonists confer a profound neuroprotective effect in animal models of Parkinson's disease. In this article, the evidence suggesting a role for glutamate receptor antagonists in the treatment of Parkinson's disease is reviewed.

THERAPEUTIC BLOCKADE OF SUBTHALAMIC OUTPUT

Degeneration of dopaminergic neurons projecting from the substantia nigra pars compacta (SNc) to the striatum results in increased activity of the striatal neurons projecting to the lateral globus pallidus (LGP), and decreased activity of striatal neurons projecting to the medial globus pallidus (MGP) and the substantia nigra pars reticulata (SNr).[8,9] These striatal efferent pathways γ-aminobutyric acid (GABA) and are inhibitory, so the activity of the LGP projection to the subthalamic nucleus (STN) is reduced, and the activities of the MGP and SNr pathways to the thalamus are increased.[10,11] The reduced activity of an inhibitory GABAergic pathway to the STN disinhibits STN neurons and causes them to be more active. The enhanced activity of the excitatory glutamatergic STN projections to MGP and SNr further increases the activity of GABAergic MGP and SNr neurons.[10,11] The net result is increased activity of inhibitory neurons in the output nuclei (MGP and SNr) of the basal ganglia and, consequently, reduced activity of thalamocortical neurons. It has

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Rationale for the Use of NMDA Antagonists in Parkinson's Disease*

- Pharmacological blockade of the abnormally increased activity of subthalamic output
- NMDA antagonists enhance the release and turnover of striatal dopamine in vivo
- NMDA antagonists reverse the akinesia and rigidity associated with monamine depletion or neuroleptic-induced catalepsy
- Subthreshold doses of NMDA antagonists synergize with dopaminergic agonists and anticholinergic drugs
- NMDA receptor blockade may account for some of the antiparkinsonian effects of amantadine and the anticholinergic drugs
- NMDA antagonists protect nigral neurons from death in the methamphetamine and MPTP models of Parkinson's disease

*NMDA indicates *N*-methyl-D-aspartate; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

been suggested that the resultant reduced thalamocortical activity accounts for parkinsonian signs.[8,10-12]

In this model of basal ganglia function, overactivity of the STN projections is postulated to play a central role in the clinical manifestations of Parkinson's disease.[8,10-12] Increased activity of STN neurons has been reported in monkeys treated with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP).[8,12] Inactivation of the STN in parkinsonian animals would be expected to reduce activity of the MGP and SNr, thereby increasing thalamocortical activity, and producing clinical improvement. In fact, ablation of the STN in MPTP-treated monkeys markedly reduces parkinsonian signs of akinesia, rigidity and tremor, as predicted by the model.[13]

Because the STN projection is glutamatergic,[14,15] pharmacological "inactivation" of this pathway may be possible with glutamate-receptor antagonists. Several distinct glutamate receptors have been identified and have been named for *N*-methyl-D-aspartate (NMDA), kainate, and quisqualate, which are the most selective agonists at each receptor type.[16,17] Of these, the NMDA receptor is the best characterized and highly specific antagonists are available. There are moderate numbers of NMDA receptors in the entopeduncular nucleus, MGP, and STN.[18] Injection of NMDA receptor antagonists into the entopeduncular nucleus (the rodent analog of MGP) or into the SNr of monoamine-depleted rats potently reverses akinesia and rigidity.[19] The STN itself receives prominent excitatory input (probably glutamatergic) from neocortex,[20] and NMDA receptors are involved in synaptic activation of STN.[21] As anticipated, the akinesia and rigidity associated with monoamine-depletion are also reversed by injection of NMDA receptor antagonists into the STN.[19]

Would systemic administration of NMDA receptor antagonists have beneficial therapeutic effects, or are these drugs only helpful when injected into discrete nuclei? The STN output to MGP and SNr is the only glutamatergic pathway that is thought to have abnormally increased activity in Parkinson's disease.[8,10-12] It is conceivable that low doses of NMDA antagonists could suppress selectively the overactivity of MGP and SNr neurons without producing the deleterious side effects expected of massive blockade of NMDA receptors elsewhere in the brain. Consistent with this hypothesis, it has been shown that systemic administration of MK-801, a noncompetitive NMDA receptor antagonist, causes a pronounced locomotor stimulation in mice or rats depleted of monoamines.[19,22] Moreover, after monoamine depletion, there is a marked synergism such that a very low systemic dose of a competitive or noncompetitive NMDA antagonist, when combined with either a muscarinic cholinergic antagonist or a subthreshold dose of levodopa, apomorphine, or SKF38393 (a selective dopamine D_1 receptor agonist), stimulates motor activity effectively.[19,23]

In contrast to these studies, however, there is a preliminary report indicating that when MK-801 was administered to a single MPTP-treated monkey, it was without therapeutic benefit.[24] The therapeutic index of MK-801 is very low, and the fact that the treated monkey was described as having "marked unresponsiveness to environmental stimuli" suggests that anesthetic doses of the drug may have been employed.[24] Additional studies using a variety of NMDA antagonists in MPTP-treated monkeys will clarify this discrepancy.

SIMILARITY OF ACTION OF DOPAMINERGIC AGONISTS AND NMDA ANTAGONISTS

Biochemical Effects

Stimulation of dopamine D_1 receptors activates adenyl cyclase and results in increased intracellular levels of cAMP.[25] This, in turn, activates cAMP-dependent protein kinase.[26] One of the substrates for this kinase is DARPP-32, a dopamine- and cAMP-regulated phosphoprotein that is enriched in striatonigral neurons.[27] Once phosphorylated, DARPP-32 becomes a potent inhibitor of protein phosphatase-1, and it has been hypothesized that the function of phospho-DARPP-32 may be to prevent dephosphorylation of other substrates in nigrostriatal neurons.[28] Activation of NMDA receptors results in dephosphorylation of DARPP-32 and, in this way, antagonizes the action of dopamine.[29,30] *N*-methyl-D-aspartate receptor antagonists prevent glutamate-induced dephosphorylation of DARPP-32 and, therefore, facilitate dopaminergic function.[29,30]

Behavioral Effects

Catalepsy (postural rigidity) can be induced in rats by administration of neuroleptics and has been used by some investigators as a model of Parkinson's disease. Neuroleptic-induced catalepsy is reversed by either dopaminergic agonists or competitive and noncompetitive NMDA receptor antagonists.[31,32] Dopaminergic agonists and NMDA receptor antagonists may also have similar effects in drug discrimination studies. Rats trained to discriminate the selective D_2 agonist, quinpirole, from saline cross-generalize to MK-801 injected intraperitoneally (D. Cory-Slechta, PhD, written communication, 1990).

The mechanism by which NMDA receptor antagonists produce behavioral effects similar to those of dopamine agonists is unknown and needs to be investigated. Conceivably, it might be related to intracellular biochemical events such as those mediated by DARPP-32.[29,30] It has also been reported by several investigators that NMDA receptor antagonists increase striatal dopamine release and turnover in vivo.[33-35] Either of these potential mechanisms would likely be beneficial in Parkinson's disease.

CURRENTLY USED MEDICATIONS AS NMDA ANTAGONISTS

It appears certain that blockade of central muscarinic receptors plays a role in the beneficial effects of anticholinergic drugs. For example, administration of a centrally active cholinesterase inhibitor increases parkinsonian symptoms, and this can be blocked by anticholinergic medications.[36] On the other hand, the doses and serum levels of these drugs appear to be excessive relative to the number and affinity of muscarinic receptors in the brain. With a total daily dose of trihexyphenidyl of only 5 mg, *trough* serum levels as high as 200 nmol/L have been reported, and trough levels increase in proportion to daily dose.[37] Peak levels of trihexyphenidyl may be as high as 1000 nmol/L (1 μmol/L) after a single 10-mg dose.[38] In dystonic patients treated with higher doses of trihexyphenidyl, trough levels may approach 2000 nmol/L (2 μmol/L).[37] As judged by positron emission tomographic scanning studies employing labeled anticholinergic drugs, these compounds penetrate the blood brain barrier easily, and it is expected that serum levels and unbound extracellular central nervous system levels would be about equivalent (K. Frey, MD, PhD, oral communication, 1990). Because the affinity of muscarinic cholinergic receptors for trihexyphenidyl is 1 nmol/L,[39] it appears that the receptors may be saturated with drug at low to moderate clinical doses.

Anticholinergic drugs are also noncompetitive antagonists of the NMDA receptor. Trihexyphenidyl (Artane), ethopropazine (Parsidol), procyclidine (Kemadrin), and diphenhydramine (Benadryl) each interact with the NMDA receptor, apparently acting at the ion channel.[40] It has been shown that procyclidine and ethopropazine compete for MK-801 binding with inhibition constants in the low micromolar range.[40] As noted above, anticholinergic drug levels in the brain may approach concentrations at which they would be expected to interact significantly with NMDA receptors. This raises the possibility that blockade of NMDA receptors by anticholinergic drugs may be important in their beneficial antiparkinsonian effects.

Other drugs used commonly in the treatment of Parkinson's disease may also have NMDA receptor antagonist properties. Memantine (1-amino-3,5-dimethyl adamantane), a dimethyl congener of amantadine, is used to treat Parkinson's disease in Europe. Like dopaminergic agonists and NMDA antagonists, memantine reverses neuroleptic-induced catalepsy.[31] Using patch clamp techniques, it has been shown that NMDA receptor ion channel currents are blocked by memantine.[41] At therapeutic concentrations, memantine also competes for MK-801 binding.[42] Amantadine (1-amino adamantane), a more commonly used adamantane derivative, modulates the sensitivity of NMDA receptor ion channel binding sites as measured by phencyclidine binding.[43] Together, these findings suggest that the therapeutic benefits of these drugs may be mediated, in part, by NMDA receptor blockade.

OTHER POTENTIAL SYMPTOMATIC BENEFITS OF NMDA ANTAGONISTS

The effects of other antiparkinsonian medications may be potentiated by NMDA receptor antagonists. When MK-801 is administered to monoamine-depleted mice in doses that are without behavioral effect, addition of an anticholinergic drug causes a marked locomotor stimulation.[23] Similarly, when subthreshold doses of MK-801 and apomorphine are given in combination to monoamine-depleted mice, there is a synergistic response and motor activity increases.[23] Most recently, it has been demonstrated that extremely low doses of competitive or noncompetitive NMDA antagonists, themselves without motor effects, shift the dose-response curve of levodopa to the left in rats depleted of monoamines.[19] In the clinical setting, low-dose NMDA antagonist therapy might provide a means of lowering the doses of other medications, or of increasing their efficacy. If oxidative products of dopamine play a role in nigral cell death,[44] low-dose NMDA antagonists may allow clinicians to decrease levodopa doses and, thereby, diminish the potential for oxidative damage.

Just as anticholinergic drugs can act as NMDA antagonists, NMDA receptor antagonists can function as "anticholinergic" agents. In the striatum, activation of NMDA receptors causes release of acetylcholine, and antagonists can effectively inhibit this release.[45,46] Decreased release of striatal acetylcholine may complement and potentiate the anticholinergic effects of direct muscarinic antagonists and provides another mechanism, by which NMDA antagonists might augment antiparkinsonian therapy.

N-methyl-D-aspartate receptor antagonists may also help to prevent or minimize the unpredictable and sometimes disabling dyskinesias associated with chronic dopaminergic agonist therapy. It has been suggested that dopamine receptor sensitization may be involved in the pathophysiology of the hyperkinetic movements that begin after long-term treatment of Parkinson's disease.[1,47] In 6-hydroxydopamine–lesioned rats, MK-801 prevents the receptor sensitization that occurs with chronic D_1 agonist treatment.[48] Thus, if receptor sensitization is important in the development of dyskinesias, NMDA antagonists may be useful adjuncts to dopaminergic agonist therapy.

NMDA ANTAGONISTS AS NEUROPROTECTIVE AGENTS IN PARKINSON'S DISEASE

Excitotoxicity mediated by activation of NMDA receptors has been implicated in the pathogenesis of chronic neurodegenerative disorders, including Huntington's disease,[49,50] amyotrophic lateral sclerosis,[51] olivopontocerebellar atrophy,[52] and Alzheimer's disease.[53,54] The ion channel of the NMDA receptor complex is gated (blocked) by magnesium in a voltage-dependent fashion.[55] When a neuron is depolarized for any reason, or if it is unable to maintain its membrane potential, the magnesium blockade is lifted and the NMDA receptor can be activated. Glucose metabolism and adenosine triphosphate production via oxidative metabolism are necessary to generate a resting membrane potential sufficient to maintain the voltage-dependent magnesium blockade of the NMDA receptor ion channel[56]; as intracellular adenosine triphosphate levels decrease, there is a concomitant decline in membrane potential. In this way, neurons that are compromised by some other process, such as defective mitochondrial energy metabolism, would be rendered more vulnerable to NMDA receptor–mediated toxicity.[57] In such compromised neurons, normal concentrations of glutamate may become lethal, and excitotoxicity might simply be the final common pathway to cell death. (Roger Albin, MD [written communication, 1990], has termed this the "weak excitotoxic hypothesis.") In this regard, the recently described defect in complex I of the mitochondrial electron transport chain in Parkinson's disease may be important.[58-60] This defect would be expected to increase the potential for excitotoxic cell damage both by increasing levels of glutamate and by indirectly reducing magnesium blockade of the ion channel.

N-methyl-D-aspartate receptor antagonists provide almost complete protection against methamphetamine-induced toxicity to the nigrostriatal dopamine pathway, a model of Parkinson's disease.[61] The anatomical site at which NMDA antagonists confer protection is unknown. More recently, it has also been shown that competitive and noncompetitive NMDA antagonists protect against MPP^+ toxicity if these agents are given throughout the period in which MPP^+ is present in the brain.[62] The NMDA antagonists are protective when administered systemically or by direct injection into the substantia nigra, suggesting that it is the substantia nigra that is the site of action of these drugs. The substantia nigra receives glutamatergic innervation from a frontal cortex and contains a moderate number of NMDA receptors.[18] The toxin MPP^+ is believed to act by specifically inhibiting complex I of the mitochondrial electron transport chain,[63] thereby creating a bioenergetic defect in nigral neurons. It seems likely that NMDA antagonists are conferring protection simply by blocking the excitotoxic final common pathway to cell death and allowing neurons to survive until the toxin (MPP^+) is no longer present. If environmental toxins or bioenergetic defects play roles in the cause of Parkinson's disease, NMDA receptor antagonists may provide a means of retarding disease progression.

POTENTIAL PROBLEMS AND FUTURE DIRECTIONS

Does the fact that certain currently used medications may have NMDA antagonist properties mean that specific NMDA antagonists will not improve the treatment of Parkinson's disease? Amantadine, memantine, and the anticholinergic agents are weak and nonspecific NMDA antagonists, and they all have effects on other neurotransmitter systems that produce dose-limiting side effects. For example, in addition to its effects on the dopamine system, amantadine has variable effects on norepinephrine, serotonin, GABA, and acetylcholine that certainly limit its use as an NMDA antagonist.[64] The anticholinergic drugs probably saturate the brain's muscarinic receptors before exerting a significant blockade of the NMDA receptor. Because the drugs used currently for Parkinson's disease interact with numerous transmitter systems, including the glutamatergic system, it is likely that intolerable side effects develop before there is significant NMDA receptor blockade. This may explain why treatment with amantadine and the anticholinergic drugs does not appear to slow disease progression. Thus, there is reason to be optimistic that *specific* NMDA antagonists may prove to be useful clinically.

Treatment of patients with NMDA receptor antagonists, however, may possibly be associated with significant side effects. Noncompetitive antagonists acting at the receptor ion channel may have psychotomimetic or dissociative anesthetic properties similar to phencyclidine (PCP) and ketamine.[65] Because the NMDA receptor is also apparently important in learning and memory functions,[66] antagonists might cause cognitive impairment. On the other hand, the potential for side effects is likely to be dependent on the type of antagonist used, and the incidence of side effects would be expected to be dose dependent. Competitive antagonists appear to have less psychotomimetic potential than noncompetitive antagonists,[67] and even MK-801, a potent noncompetitive blocker, did not produce psychosis when administered to humans with epilepsy.[68] Moreover, animal studies indicate that extremely low doses of NMDA antagonists may produce a potent and clinically useful synergy with commonly used anticholinergic and dopaminergic agonist drugs.[19,23] Thus, it may be possible to use selective NMDA antagonists therapeutically without encountering intolerable side effects.

Both basic and preclinical studies must be performed before NMDA receptor antagonists are used in patients with Parkinson's disease. Although some investigators have found no NMDA receptor changes with chronic in vivo antagonist treatment (A. B. Young, MD, PhD, oral communication, 1990), it has been reported that treatment of primary neuronal cultures with competitive antagonists may increase the number of MK-801 binding sites (P. Molinoff, MD, oral communication, 1990). Because the clinical impact of increased numbers of NMDA receptors might be enhanced excitotoxic potential as well as symptomatic decline, the chronic effects of antagonists on the NMDA receptor complex must be defined unambiguously.

Administration of both competitive and noncompetitive NMDA antagonists has been associated with acute, reversible vacuolization in certain neurons of the cingulate and retrosplenial cortex in rats,[69] but the vacuolization subsides within 24 to 48 hours. This phenomenon appears to be self-limited, its functional significance is not clear,[70] and it can be prevented by co-administration of anticholinergic agents.[71] Despite the apparent benign nature of these changes, the issue of antagonist-associated vacuolization warrants further investigation prior to initiation of large-scale clinical trials.

It will be of interest to examine whether the increased activity of the subthalamic nucleus results in significant regulatory changes in glutamate receptors in MGP and SNr of MPTP-treated monkeys and patients with Parkinson's disease. Receptor down-regulation might alter the effectiveness of antagonist drugs. The mechanisms of interaction of anticholinergic drugs and amantadine with the NMDA receptor/ion channel complex remain to be explored in detail, and it would be useful to assess drug levels in cerebrospinal fluid of patients treated with these agents. At the preclinical level, it will be important to evaluate the efficacy of a variety of competitive and noncompetitive NMDA antagonists in reducing parkinsonian symptoms in MPTP-treated monkeys prior to beginning human trials. Whether low doses of NMDA antagonists produce synergistic effects with anticholinergics and dopaminergic agonists in parkinsonian monkeys must also be determined. It will also be of interest to evaluate the antiparkinsonian efficacy of antagonists of non-NMDA glutamate receptors. Initial studies of a quisqualate receptor antagonist in MPTP-induced parkinsonian *Rhesus* monkeys indicate that this class of drug has potent and dramatic antiparkinsonian properties when administered systemically.[72]

CONCLUSION

More effective symptomatic and neuroprotective therapies are needed urgently for Parkinson's disease. This review of the current literature on NMDA receptor antagonists in relation to Parkinson's disease makes a strong case for the use of these agents as an adjunct to current antiparkinsonian therapies. There are several reasons to believe that NMDA antagonists will provide symptomatic relief; in fact, the benefits derived from certain commonly used antiparkinsonian medications may be related to their ability to block NMDA receptors. Moreover, the neuroprotective properties of NMDA antagonists may allow clinicians to slow disease progression and delay disability by blocking the final common pathway that leads to nigral cell death. Although NMDA receptor antagonists may prove to be useful in this disorder, these drugs should be used in patients only after sufficient supportive data has been amassed from preclinical studies. It is hoped that this speculative review will stimulate research in this important area, and lead ultimately to better treatments for our patients with Parkinson's disease.

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References

1. Cedarbaum JM. Pharmacokinetic and pharmacodynamic considerations in management of motor response fluctuations in Parkinson's disease. *Neurol Clin*. 1990;8:31-49.
2. Kurlan R. Practical therapy of Parkinson's disease. *Semin Neurol*. 1987;7:160-166.
3. Comella CL, Tanner CM. Anticholinergic drugs in the treatment of Parkinson's disease. In: Koller WC, Paulson G, eds. *Therapy of Parkinson's Disease*. New York, NY: Marcel Dekker Inc; 1990:123-141.
4. Cotzias GC, VanWoert MH, Schiffer LM. Aromatic amino acids and modification of parkinsonism. *N Engl J Med*. 1967;276:374-379.
5. Ehringer H, Hornykiewicz O. Verteilung von Noradrenalin und Dopamin (3-Hydroxytyramin) im Gehirn des Menschen und ihr Verhalten bei Erkrankungen des extrapyramidalen Systems. *Klin Wochenschr*. 1960;38:1236-1239.
6. Jankovic J, Marsden CD. Therapeutic strategies in Parkinson's disease. In: Jankovic J, Tolosa E, eds. *Parkinson's Disease and Movement Disorders*. Baltimore, Md: Urban & Schwarzenberg; 1988:95-119.
7. Parkinson Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's

disease. *N Engl J Med.* 1989;46:1052-1060.

8. Miller WC, DeLong MR. Altered tonic activity of neurons in the globus pallidus and subthalamic nucleus in the primate MPTP model of parkinsonism. In: Carpenter MB, Jayarman A, eds. *The Basal Ganglia II.* New York, NY: Plenum Press; 1987:415-427.

9. Pan HS, Walters JR. Unilateral lesion of the nigrostriatal pathway decreases the firing rate and alters the firing pattern of globus pallidus neurons in the rat. *Synapse.* 1988;2:650-659.

10. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *Trends Neurosci.* 1989;12:366-375.

11. Klockgether T, Turski L. Excitatory amino acids and the basal ganglia: implications for the therapy of Parkinson's disease. *Trends Neurosci.* 1989;12:285-286.

12. Mitchell IJ, Clarke CE, Boyce S, Robertson RG, et al. Neural mechanisms underlying parkinsonian symptoms based upon regional uptake of 2-deoxyglucose in monkeys exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. *Neuroscience.* 1989;32:213-226.

13. Bergman H, Wichmann T, DeLong MR. Reversal of experimental parkinsonism by lesions of the subthalamic nucleus. *Science.* 1990;249:1436-1438.

14. Albin RL, Aldridge JW, Young AB, Gilman S. Feline subthalamic nucleus neurons contain glutamate-like but not GABA-like or glycine-like immunoreactivity. *Brain Res.* 1989;491:185-188.

15. Smith Y, Parent A. Neurons of the subthalamic nucleus in primates display glutamate but not GABA immunoreactivity. *Brain Res.* 1988;453:353-356.

16. Watkins JC, Evans RH. Excitatory amino acid transmitters. *Annu Rev Pharmacol Toxicol.* 1981;21:165-204.

17. Dingledine R, Boland LM, Chamberlin NL, et al. Amino acid receptors and uptake systems in the mammalian central nervous system. *Crit Rev Neurobiol.* 1988;4:1-96.

18. Albin RL, Makowiec RL, Hollingsworth Z, et al. Excitatory amino acid receptors in rat basal ganglia. *Soc Neurosci Abstr.* 1990;16:1233. Abstract.

19. Klockgether T, Turski L. NMDA antagonists potentiate antiparkinsonian actions of L-dopa in monoamine-depleted rats. *Ann Neurol.* 1990;28:539-546.

20. Afsharpour S. Topographical projections of the cerebral cortex to the subthalamic nucleus. *J Comp Neurol.* 1985;236:14-28.

21. Nakanishi H, Kita H, Kitai ST. An *N*-methyl-D-aspartate receptor mediated excitatory postsynaptic potential evoked in subthalamic neurons in an in vitro slice preparation of the rat. *Neurosci Lett.* 1988;95:130-136.

22. Carlsson M, Carlsson A. The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. *J Neural Transm.* 1989;75:221-226.

23. Carlsson M, Carlsson A. Interactions between glutamatergic and monoaminergic systems within the basal ganglia: implications for schizophrenia and Parkinson's disease. *Trends Neurosci.* 1990;13:272-276.

24. Crossman AR, Peggs D, Boyce S, et al. Effect of the NMDA antagonist MK-801 on MPTP-induced parkinsonism in the monkey. *Neuropharmacology.* 1989;28:1271-1273.

25. Kebabian JW, Calne DB. Multiple receptors for dopamine. *Nature.* 1979;277:93-96.

26. Nairn AC, Hemmings HC Jr, Greengard P. Protein kinases in the brain. *Annu Rev Biochem.* 1985;54:931-976.

27. Ouimet CC, Miller PE, Hemmings HC Jr, et al. DARPP-32, a dopamine and adenosine 3′,5′-monophosphate-regulated phosphoprotein enriched in dopamine-innervated brain regions, III: immunocytochemical localization. *J Neurosci.* 1984;4:111-124.

28. Hemmings HC Jr, Greengard P, Tung HYL, Cohen P. DARPP-32, a dopamine-regulated neuronal phosphoprotein, is a potent inhibitor of protein phosphatase-1. *Nature.* 1984;310:503-505.

29. Halpain S, Girault J-A, Greengard P. Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. *Nature.* 1990;343:369-372.

30. Girault J-A, Halpain S, Greengard P. Excitatory amino acid antagonists and Parkinson's disease. *Trends Neurosci.* 1990;13:325-326.

31. Schmidt WJ, Bubser M, Hauber W. Excitatory amino acids and Parkinson's disease. *Trends Neurosci.* 1990;13:46-47.

32. Schmidt WJ, Bubser M. Anticataleptic effects of the N-methyl-D-aspartate antagonist MK-801 in rats. *Pharmacol Biochem Behav.* 1989;32:621-623.

33. Gruen RJ, Roth RH, Bunney BS, Moghaddam B. Increase in striatal dopamine release following local perfusion of the NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid. *Soc Neurosci Abstr.* 1990;16:679. Abstract.

34. Bennett JP Jr, Leslie CA. NMDA receptors modulate striatal dopamine release and metabolism in vivo: a microdialysis study. *Soc Neurosci Abstr.* 1990;16:679. Abstract.

35. Imperato A, Jensen LH, Alivernini L, et al. The effect of selective agonists and antagonists of excitatory amino acid receptors on dopaminergic and cholinergic neurotransmission in awake rats: possible clinical implications. *Soc Neurosci Abstr.* 1990;16:679. Abstract.

36. Duvoisin RC. Cholinergic-anticholinergic antagonism in parkinsonism. *Arch Neurol.* 1967;17:124-136.

37. Burke RE, Fahn S. Serum trihexyphenidyl levels in the treatment of torsion dystonia. *Neurology.* 1985;35:1066-1069.

38. Burke RE, Fahn S. Pharmacokinetics of trihexyphenidyl after short-term and long-term administration to dystonic patients. *Ann Neurol.* 1985;18:35-40.

39. Burke RE. The relative selectivity of anticholinergic drugs for the M1 and M2 muscarinic subtypes. *Mov Disord.* 1986;1:135-144.

40. Olney JW, Price MT, Labruyere J, et al. Anti-parkinsonian agents are phencyclidine agonists and *N*-methyl-D-aspartate antagonists. *Eur J Pharmacol.* 1987;142:319-320.

41. Bormann J. Memantine is a potent blocker of *N*-methyl-D-aspartate (NMDA) receptor channels. *Eur J Pharmacol.* 1989;166:591-592.

42. Kornhuber J, Bormann J, Retz W, et al. Memantine displaces [^{3}H]MK-801 at therapeutic concentrations in postmortem human frontal cortex. *Eur J Pharmacol.* 1989;166:589-590.

43. Quirion R, Pert CB. Amantadine modulates phencyclidine binding site sensitivity in rat brain. *Experientia.* 1982;38:955-956.

44. Olanow CW. Oxidation reactions in Parkinson's disease. *Neurology.* 1990;40(suppl 3):32-37.

45. Snell LD, Johnson KM. Antagonism of *N*-methyl-D-aspartate-induced transmitter release in the rat striatum by phencyclidine-like drugs and its relationship to turning behavior. *J Pharmacol Exp Ther.* 1985;235:50-57.

46. Lehmann J, Scatton B. Characterization of the excitatory amino acid receptor-mediated release of [^{3}H]acetylcholine from rat striatal slices. *Brain Res.* 1982;252:77-89.

47. Mouradian MM, Chase TN. Hypothesis: central mechanisms and levodopa response fluctuations in Parkinson's disease. *Clin Neuropharmacol.* 1988;11:378-385.

48. Criswell HE, Mueller RA, Breese GR. Long-term D1-dopamine receptor sensitization in neonatal 6-OHDA-lesioned rats is blocked by an NMDA antagonist. *Brain Res.* 1990;512:284-290.

49. Beal MF, Kowall NW, Ellison DW, et al. Replication of the neurochemical characteristics of Huntington's disease by quinolinic acid. *Nature.* 1986;321:168-172.

50. Young AB, Greenamyre JT, Hollingsworth Z, et al. NMDA receptor losses in putamen from patients with Huntington's disease. *Science.* 1988;241:981-983.

51. Plaitakis A. Glutamate dysfunction and selective motor neuron degeneration in amyotrophic lateral sclerosis: a hypothesis. *Ann Neurol.* 1990;28:3-8.

52. Plaitakis A, Berl S, Yahr MD. Abnormal glutamate metabolism in adult-onset degenerative neurological disorder. *Science.* 1982;216:193-196.

53. Greenamyre JT, Young AB. Excitatory amino acids and Alzheimer's disease. *Neurobiol Aging.* 1989;10:593-602.

54. Greenamyre JT. Neuronal bioenergetic defects, excitotoxicity and Alzheimer's disease: 'use it and lose it.' *Neurobiol Aging.* 1991;12:334-336.

55. Nowak L, Bregestovski P, Ascher P, et al. Magnesium gates glutamate-activated channels in mouse central neurones. *Nature.* 1984;307:462-466.

56. Henneberry RC. The role of neuronal energy in the neurotoxicity of excitatory amino acids. *Neurobiol Aging.* 1989;10:611-613.

57. Novelli A, Reilly JA, Lysko PG, Henneberry RC. Glutamate becomes neurotoxic via the NMDA receptor when intracellular energy levels are reduced. *Brain Res.* 1988;451:205-212.

58. Mizuno Y, Ohta S, Tanaka M, et al. Deficiencies in complex I subunits of the respiratory chain in Parkinson's disease. *Biochem Biophys Res Commun.* 1989;163:1450-1455.

59. Parker WD Jr, Boyson SJ, Parks JK. Abnormalities of the electron transport chain in idiopathic Parkinson's disease. *Ann Neurol.* 1989;26:719-723.

60. Schapira AHV, Cooper JM, Dexter D, et al. Mitochondrial complex I deficiency in Parkinson's disease. *Lancet.* 1989;1:1269.

61. Sonsalla PK, Nicklas WJ, Heikkila RE. Role for excitatory amino acids in methamphetamine-induced nigrostriatal dopaminergic toxicity. *Science.* 1989;243:398-400.

62. Turski L, Bressler K, Rettig K-J, et al. *N*-methyl-D-aspartate antagonists protect substantia nigra from MPP$^+$ toxicity. *Ann Neurol.* 1990;28:295. Abstract.

63. Kindt MV, Nicklas WJ, Sonsalla PK, Heikkila RE. Mitochondria and the neurotoxicity of MPTP. *Trends Pharmacol Sci.* 1986;7:473-475.

64. Allen RM. Role of amantadine in the management of neuroleptic induced extrapyramidal syndromes: overview and pharmacology. *Clin Neuropharmacol.* 1983;6(suppl 1):64-73.

65. Koek W, Woods JH, Winger JD. MK-801, a proposed noncompetitive antagonist of excitatory amino acid neurotransmission, produces phencyclidine-like behavioral effects in pigeons, rats and rhesus monkeys. *J Pharmacol Exp Ther.* 1988;245:969-974.

66. Morris RGM, Anderson E, Lynch GS, Baudry M. Selective impairment of learning and blockade of long-term potentiation by an *N*-methyl-D-aspartate receptor antagonist. *Nature.* 1986;319:774-776.

67. Woods JH, Koek W, Ornstein P. A preliminary study of PCP-like behavioral effects of 2-amino-5-phosphonovalerate in rhesus monkey. In: Hicks TP, Lodge D, McLennan H, eds. *Excitatory Amino Acid Transmission.* New York, NY: Alan R Liss; 1987:205-212.

68. Troupin AS, Mendius JR, Cheng F, Risinger MW. MK-801. In: Meldrum BS, Porter RJ, eds. *Current Problems in Epilepsy.* London, England: John Libbey; 1986;4:191-201.

69. Olney JW, Labruyere J, Price MT. Pathological changes induced in cerebrocortical neurons by phencyclidine and related drugs. *Science.* 1989;244:1360-1362.

70. Allen HW, Iversen LL. Phencyclidine, dizocilpine, and cerebrocortical neurons. *Science.* 1990;247:221.

71. Olney JW, Labruyere J, Wang GJ, Price MT. Anticholinergics prevent neurotoxic side effects of NMDA antagonists. *Soc Neurosci Abstr.* 1990;16:1122. Abstract.

72. Greenamyre JT, Zhang ZM, Gash DM, Kurlan RK, Turski L. A glutamate antagonist, NBQX, has antiparkinsonian effects in MPTP-treated monkeys. *Neurology.* 1991;41:1163. Abstract.

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Observations

Unilateral Oculomotor Palsy and Bilateral Ptosis From Paramedian Midbrain Infarction

Grant T. Liu, MD; Enrique J. Carrazana, MD; Michael E. Charness, MD

• Lesions of the oculomotor fascicles are localized clinically by associated neurologic deficits. We present two patients with bilateral ptosis, unilateral paresis of all other muscles innervated by the oculomotor nerve, and sparing of the contralateral superior rectus muscle—findings suggesting a lesion of the proximal oculomotor fascicles and the central caudal subnucleus. To our knowledge, these are the first such cases with radiologic confirmation of a lesion within the dorsal, paramedian midbrain.

(*Arch Neurol.* 1991;48:983-986)

The oculomotor fascicles sweep ventrally and laterally from the oculomotor complex, pass through and medial to the red nucleus, and converge to exit the brain stem medial to the cerebral peduncles.[1] The clinical localization of lesions along the dorsal-ventral course of the oculomotor fascicles relies on associated neurologic findings. Damage to the ventral fascicles and the nearby cerebral peduncle causes ipsilateral third-nerve palsy and contralateral hemiparesis (Weber's syndrome).[2] Involvement of fascicles within the red nucleus leads to oculomotor palsy with contralateral involuntary movements (Benedikt's syndrome). Extension of such a lesion to the brachium conjunctivum produces additional contralateral ataxia (Claude's syndrome).[2] When sufficiently small, fascicular lesions can mimic complete or partial extra-axial third-nerve palsies.[3-8] Most of these have been located in the ventral midbrain, sparing the red nucleus and cerebral peduncles.

Small lesions of the proximal oculomotor fascicles have been reported only rarely.[5,8] Extension of such a lesion would involve the oculomotor subnuclei, the medial longitudinal fasciculus, and the mesencephalic reticular formation, causing ipsilateral oculomotor paresis and combinations of bilateral ptosis, bilateral superior rectus palsy, internuclear ophthalmoplegia, and lethargy.[2,9] We present two patients in whom focal infarction of the dorsal, paramedian midbrain led to a unique syndrome of pupil-sparing oculomotor palsy, lethargy, and bilateral ptosis, without affecting the contralateral superior rectus.

REPORT OF CASES

CASE 1.—A 46-year-old man developed double vision, bilateral ptosis, and lethargy immediately after a percutaneous transluminal coronary angioplasty for a complete right coronary artery occlusion. The patient had a history of recent myocardial infarction and hypercholesterolemia. Examination revealed pronounced bilateral ptosis in the setting of mild inattention and drowsiness. He could open his eyes only by lifting his lids manually. Visual acuity with correction was J1 OD and J2 OS. Visual fields by confrontation were normal. A small cotton wool exudate was noted along the superotemporal arcade in the left fundus. The pupils were equal, round, and reactive to light. In primary position the left eye deviated outward and downward. There was markedly decreased adduction and elevation of the left eye, and downward gaze was diminished on abduction. Attempted adduction of the left eye was accompanied by abducting nystagmus of the right eye. All movements of the right eye were normal. The remainder of his neurologic examination was normal. Magnetic resonance imaging (48 hours after the event) showed a small focus of increased T_2 signal in the left periaqueductal gray matter overlapping the left medial longitudinal fasciculus and caudal third-nerve nucleus (Fig 1). Two small punctate foci of increased T_2 signal were seen in the deep white matter of the right parietal and frontal lobes.

Over the first 48 hours right-sided ptosis resolved and left-sided ptosis improved considerably. Four days after the event he showed left-sided ptosis and diminished function of the left medial, superior, and inferior rectus and inferior oblique muscles with normal eye movements on the right side, except for abducting nystagmus on right horizontal gaze (Fig 2). Abduction and elevation of the left eye improved gradually over the subsequent week. After 6 weeks he had diplopia with occasional fused vision, mild left-sided ptosis with superior and medial rectus paresis, and a mild left-sided internuclear ophthalmoplegia. One month later transient diplopia was present only on sudden upgaze or with fatigue.

CASE 2.—A 31-year-old, previously healthy woman came to the hospital on January 16, 1990, complaining of sudden dizziness, difficulty seeing, and droopy eyelids. She smoked cigarettes and took oral contraceptives. Her blood pressure was 110/80 mm Hg and her heart rate was 60 beats per minute and regular. There were no heart murmurs. She was drowsy and inattentive but easily arousable. Her visual fields and acuity were normal. There was bilateral ptosis, which was worse on the left side. In primary position the left eye deviated outward and downward. Movements of the right eye were normal without abducting nystagmus. The left eye could not adduct and had only 30° of upward gaze and 45° of downward gaze. The pupils were 2 mm bilaterally and briskly reactive to light. She had mild right face and arm weakness, right-sided hyperreflexia, and truncal as well as gait ataxia.

The hematocrit, erythrocyte sedimentation rate, prothrombin time, partial thromboplastin time, and protein C, protein S, and antithrombin III levels were all normal. Results of laboratory studies revealed that the cerebrospinal fluid contained the following values: white blood cells, 0.006×10^9/L ($6/mm^3$) (lymphocytes, 0.91 [91]; mononuclear leukocytes, 0.05 [5]); red blood cells, 1×10^{12}/L ($1/mm^3$); glucose, 3.4 mmol/L (62 mg/dL); and protein 0.46 g/L (46 mg/dL). Rapid plasma reagin and antinuclear antibody were negative. Echocardiogram and 24-hour Holter monitor were normal. Magnetic resonance imaging 1 day after the event demonstrated three foci of increased T_2 signal in the left side of the midbrain: one located in the periaqueductal gray, one lateral to the red nucleus, and the third in the lateral portion of the cerebral penduncle (Fig 3). She was much more alert 2 days after admission. One week later, right-sided ptosis had resolved almost completely, left vertical gaze was improved, but she still showed mild left-sided ptosis and had only 10° of adduction.

COMMENT

Both patients had focal infarcts of the dorsal midbrain in the territory of the perforating paramedian branches of the proximal posterior cerebral artery (mesencephalic artery).[9,10] Biller and

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colleagues[11] described a man who, like patient 1, developed a midbrain stroke after percutaneous transluminal coronary angioplasty. In Dawson and Fischer's[12] review of the neurologic complications of cardiac catheterization, five of 10 affected patients developed pontine and mesencephalic dysfunction, most likely as a result of artery-to-artery embolization. They postulated that catheter-induced trauma to the aorta or to the origin of the vertebral, inominate, or subclavian arteries might cause embolization preferentially to the vertebrobasilar circulation. Patient 1 had evidence for embolization in both the anterior and posterior circulations, involving the midbrain, retina, frontal lobe, and parietal lobe. Patient 2 likely suffered a thrombotic stroke as a consequence of her use of oral contraceptives and cigarettes, two additive risk factors for thrombosis.[13] The sudden onset of symptoms, improvement within days, and cerebrospinal fluid profile were consistent with infarction, and a search for other causes, short of angiography, was unrevealing.

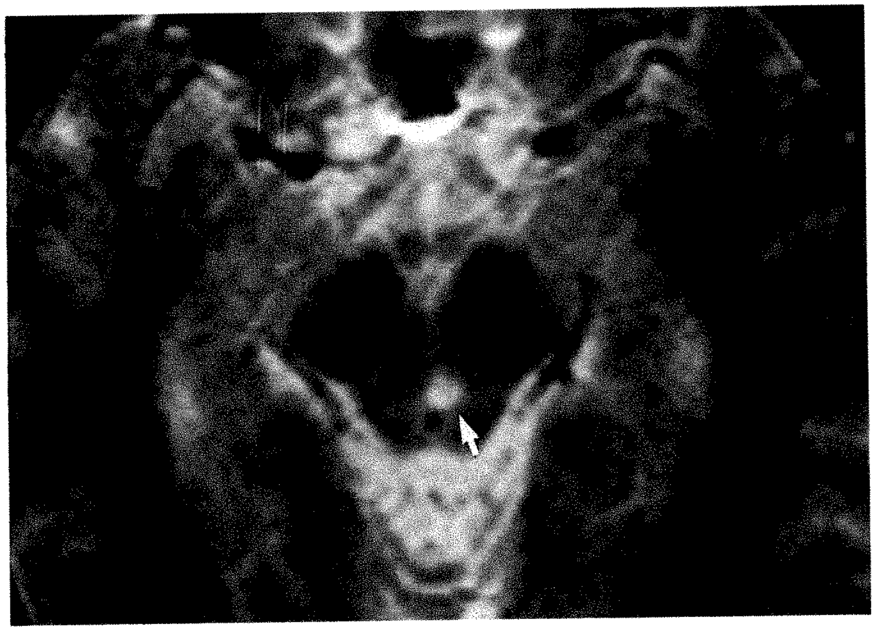

Fig 1.—Magnetic resonance imaging (TR = 2000 milliseconds, TE = 80 milliseconds) of the midbrain in patient 1, 2 days after his infarct. A single area of increased T_2 signal (arrow) is seen in the left paramedian midbrain involving the caudal portion of the oculomotor nucleus, the medial longitudinal fasciculus, and the periaqueductal gray matter.

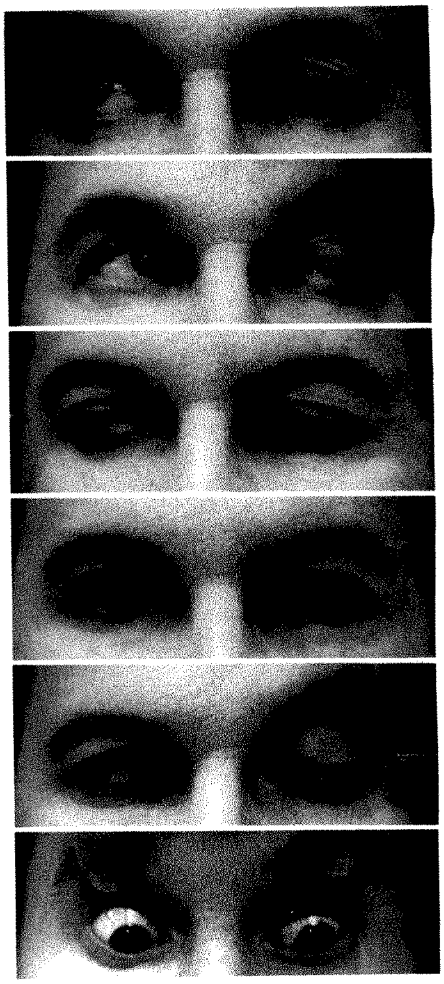

Fig 2.—Eye movements in patient 1, 4 days after his infarct. All of the abnormalities are in the left eye, including ptosis, diminished elevation on right and left upward gaze, and mildly diminished adduction and depression. By this time the right-sided ptosis had resolved and the left-sided ptosis, adduction, and depression had improved considerably.

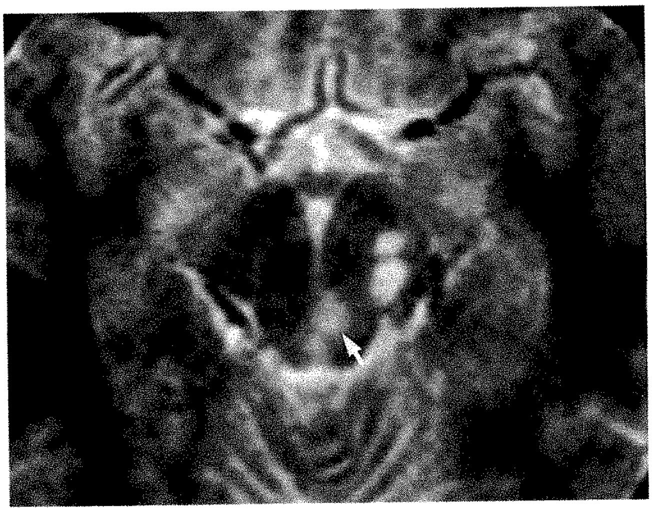

Fig 3.—Magnetic resonance imaging (TR = 2000 milliseconds; TE = 80 milliseconds) of the midbrain in patient 2, 1 day after her infarct. Three discrete regions of increased T_2 signal are seen. The left paramedian lesion (arrow) is nearly identical to that of patient 1 (Fig 2). Additional lesions in the left lateral peduncle and lateral to the red nucleus should spare the third-nerve fascicles, which course through and medial to the red nucleus before exiting the brain stem in the interpeduncular fossa.

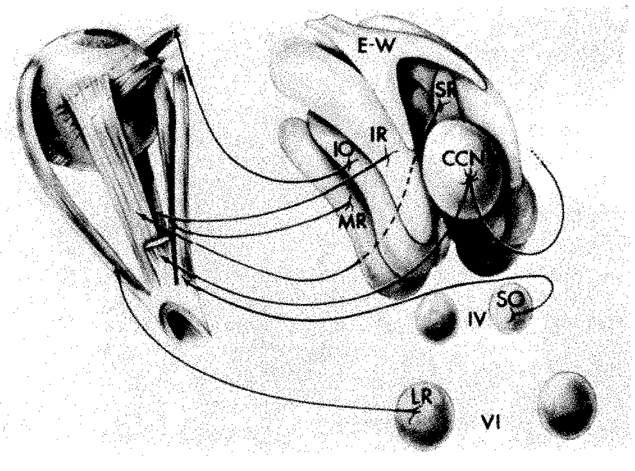

Fig 4.—Anatomy of the oculomotor complex, as proposed by Warwick.[14] The superior rectus (SR) muscle is innervated by a contralateral subnucleus. The central caudal nucleus (CCN) innervates both levator palpebrae muscles. The Edinger-Westphal subnucleus (E-W) and subnuclei for the inferior rectus (IR), inferior oblique (IO), and medial rectus (MR) muscle are arranged ipsilaterally. SO indicates superior oblique; LR, lateral rectus; and nuclei of the fourth (IV) and sixth (VI) cranial nerves (reproduced from reference 20 as modified from Warwick,[14] with permission from Wiley-Liss).

Ocular findings in these two patients were confined to extraocular muscles innervated by the left third nerve: superior, medial, and inferior rectus, inferior oblique, and levator palpebrae. In both cases, ptosis was bilateral and asymmetric, being worse ipsilateral to the ophthalmoparesis. The pupils were spared and all movements of the right eye were normal to bedside examination. (It is conceivable that minor involvement of the right superior rectus muscle might have been detected using more sensitive methods, such as Lancaster testing.) Within 1 week, both patients showed only left-sided abnormalities, including ptosis, decreased elevation, and impaired adduction, the latter due to an internuclear ophthalmoplegia in patient 1 and a medial rectus palsy in patient 2.

The selective involvement of oculomotor function and the relative paucity of additional neurologic signs suggests that both patients suffered small lesions of the paramedian midbrain. Bilateral ptosis is the hallmark of involvement of the central caudal subnucleus and localizes the lesions to the caudal oculomotor complex and its immediate vicinity.[2,14-17] The preservation of pupillary function implies sparing of the Edinger-Westphal complex and serves to delimit the dorsal and rostral extent of the nuclear lesion.[14] The internuclear ophthalmoplegia in patient 1 indicates involvement of the left medial longitudinal fasciculus, adjacent to the oculomotor complex, and drowsiness in both patients could be explained by transient disconnection of the midline midbrain reticular formation from the thalamus.[9]

This clinical neuroanatomic localization was confirmed by magnetic resonance imaging, which disclosed a small lesion in the dorsal paramedian midbrain in each patient. Although patient 2 had two additional lesions in the ventral midbrain, it is doubtful that these contributed significantly to her oculomotor deficit since both were lateral to the third-nerve fascicles.[17] The lesion involving the left cerebral peduncle likely explains her right hemiparesis, whereas that lateral to the left red nucleus could have caused her ataxia by interrupting fibers from the superior cerebellar peduncle in the dentatorubrothalamic tract.[18,19]

According to Warwick's[14] scheme for the subdivisions of the oculomotor nuclei, the midline central caudal nucleus supplies both levator palpebrae muscles, and each superior rectus muscle is innervated by a contralateral subnucleus (Fig 4). Ipsilateral subnuclei subserve the remaining extraocular muscles innervated by the third nerve and the parasympathetic pupillary constrictor fibers.[14,20] Bienfang[21] demonstrated that axons from each superior rectus subnucleus cross the midline and pass through the contralateral subnucleus before reaching the opposite third nerve. Unilateral lesions of the oculomotor complex should therefore cause bilateral ptosis, ipsilateral mydriasis, ipsilateral palsy of the medial rectus, inferior rectus, and inferior oblique muscles, and bilateral superior rectus palsy.[2,11,17,21-23]

A small number of patients have been described in whom dorsal paramedian midbrain lesions have caused bilateral ptosis and ipsilateral oculomotor paresis.[15,16,22-24] When present, involvement of the superior rectus has been either bilateral, from a nuclear lesion,[16,22,23] or contralateral, from a supranuclear lesion.[24] Our patients are unique because oculomotor paresis and bilateral ptosis were unaccompanied by significant involvement of the contralateral superior rectus muscle. Although Caplan[25] briefly mentioned two patients with bilateral ptosis, complete ophthalmoplegia on one side, and "(no) other signs of third nerve deficit" on the other side, there was neither radiologic nor pathologic confirmation of the suspected midbrain lesion.

How could a lesion of the dorsal paramedian midbrain produce bilateral ptosis and ipsilateral elevator palsy? The central caudal and superior rectus subnuclei are adjacent structures.[14] If the elevator palsy, like the bilateral ptosis, was caused by a nuclear lesion, then the superior rectus subnucleus would have to have been uncrossed, contradicting anatomic studies in several mammalian species.[14,21,26-28] More likely, the elevator palsy was supranuclear or infranuclear.

Ipsilateral[29] and contralateral[24,30] midbrain lesions have been reported to cause monocular, supranuclear paresis of elevation, presumably by interrupting axons from the rostral interstitial nucleus of the medial longitudinal fasciculus, which is believed to mediate upgaze.[29] However, in our patients, paresis of the superior rectus and inferior oblique muscles was distinguished by hypotropia in primary gaze, typically absent in a supranuclear lesion.[29] Hence, the most likely explanation for their ipsilateral elevator palsy is a lesion in the oculomotor fascicles. The pattern of recovery suggests that the major damage was infranuclear; contralateral ptosis resolved within a few days, leaving unilateral ptosis and ipsilateral elevator palsy (Fig 2). These findings support the proposal that axons destined for the superior rectus, inferior oblique, and levator palpebrae muscles segregate dorsolaterally within the oculomotor fascicles.[1,7,31]

Precise anatomic correlation of this oculomotor disorder ultimately requires postmortem examination. Nonetheless, the nearly identical clinical and magnetic resonance findings in these two patients delineate a new syndrome of the proximal oculomotor fascicles. The sudden onset of lethargy, bilateral ptosis, and ipsilateral third-nerve palsy, with sparing of the contralateral superior rectus should suggest a lesion of the dorsal paramedian midbrain, including the proximal oculomotor fascicles and the adjacent central caudal subnucleus.

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References

1. Castro O, Johnson LN, Mamourian AC. Isolated inferior oblique paresis from brain-stem infarction: perspective on oculomotor fascicular organization in the ventral midbrain tegmentum. *Arch Neurol.* 1990;47:235-237.
2. Miller NR. *Walsh and Hoyt's Clinical Neuro-ophthalmology.* 4th ed. Baltimore, Md: Williams & Wilkins; 1985:657-663.
3. Nadeau SE, Trobe JD. Pupil sparing in oculomotor palsy: a brief review. *Ann Neurol.* 1983;13:143-148.
4. Keane JR. Isolated brain-stem third nerve palsy. *Arch Neurol.* 1988;45:813-814.
5. Ksiazek SM, Repka MX, Maguire A, et al. Division oculomotor nerve paresis caused by intrinsic brainstem disease. *Ann Neurol.* 1989;26:714-718.
6. Collard M, Saint-Val C, Mohr M, Kiesmann M. Paralysie isolée du nerf moteur oculaire commun par infarctus de ses fibrès fasciculaires. *Rev Neurol.* 1990;146:128-132.
7. Hriso E, Miller A, Masdeu JC. Monocular elevation weakness and ptosis: an oculomotor fascicular syndrome? *Neurology.* 1990;40(suppl 1):309-310.
8. Hopf HC, Gutmann L. Diabetic 3rd nerve palsy: evidence for a mesencephalic lesion. *Neurology.* 1990;40:1041-1045.
9. Segarra JM. Cerebral vascular disease and behavior, I: the syndrome of the mesencephalic artery (basilar artery bifurcation). *Arch Neurol.* 1970;22:408-418.
10. Sieben G, De Reuck J, Vander Eecken H. Thrombosis of the mesencephalic artery: a clinicopathological study of two cases and its correlation with the arterial vascularisation. *Acta Neurol Belg.* 1977;77:151-162.
11. Biller J, Shapiro R, Evans LS, Haag JR, Fine M. Oculomotor nuclear complex infarction: clinical and radiological correlation. *Arch Neurol.* 1984;41:985-987.
12. Dawson DM, Fischer EG. Neurologic complications of cardiac catheterization. *Neurology.* 1977;27:496-497.
13. Longstreth WT, Swanson PD. Oral contraceptives and stroke. *Stroke.* 1984;15:747-750.
14. Warwick R. Representation of the extraocular muscles in the oculomotor nuclei of the monkey. *J Comp Neurol.* 1953;98:449-495.
15. Stevenson GC, Hoyt WF. Metastasis to midbrain from mammillary carcinoma. *JAMA.* 1963;186:514-516.
16. Growdon JH, Winkler GF, Wray SH. Midbrain ptosis: a case with clinicopathologic correlation. *Arch Neurol.* 1974;30:179-181.
17. Miller NR. *Walsh and Hoyt's Clinical Neuro-ophthalmology.* 4th ed. Baltimore, Md: Wil-

liams & Wilkins; 1985:568-570.

18. Carpenter MB. Functional relationships between the red nucleus and the brachium conjunctivum: physiologic study of lesions of the red nucleus in monkeys with degenerated superior cerebellar brachia. *Neurology.* 1957;7:427-437.

19. Felice K, Keilson GR, Schwartz WJ. 'Rubral' gait ataxia. *Neurology.* 1990;40:1004-1005.

20. Glaser JS, Bachynski B. Infranuclear disorders of eye movement. In: Glaser JS, ed. *Neuro-ophthalmology.* Philadelphia, Pa: JB Lippincott; 1990:363.

21. Bienfang DC. Crossing axons in the third nerve nucleus. *Invest Ophthalmol.* 1975;14:927-931.

22. Bogousslavsky J, Regli F. Nuclear and prenuclear syndromes of the oculomotor nerve. *Neuro-ophthalmol.* 1983;3:211-216.

23. Zackon DH, Sharpe JA. Midbrain paresis of horizontal gaze. *Ann Neurol.* 1984;16:495-504.

24. Bogousslavsky J, Regli F, Ghika J, Hungerbuhler JP. Internuclear ophthalmoplegia, prenuclear paresis of contralateral superior rectus, and bilateral ptosis. *J Neurol.* 1983;230:197-203.

25. Caplan LR. Ptosis. *J Neurol Neurosurg Psychiatry.* 1974;37:1-7.

26. Buttner-Ennever JA, Grob P, Akert K. A transsynaptic autoradiographic study of the pathways controlling the extraocular eye muscles, using $[^{125}I]B\text{-}II_b$ tetanus toxin fragment. *Ann N Y Acad Sci.* 1981;374:154-170.

27. Porter JD, Guthrie BL, Sparks DL. Innervation of monkey extraocular muscles: localization of sensory and motor neurons by retrograde transport of horseradish peroxidase. *J Comp Neurol.* 1983;218:208-219.

28. Gacek RR. Localization of neurons supplying the extraocular muscles in the kitten using horseradish peroxidase. *Exp Neurol.* 1974;44:381-403.

29. Ford CS, Schwartze GM, Weaver RG, Troost BT. Monocular elevation paresis caused by an ipsilateral lesion. *Neurology.* 1984;34:1264-1267.

30. Lessell S. Supranuclear paralysis of monocular elevation. *Neurology.* 1975;25:1134-1136.

31. Abdollah A, Francis GS. Intraaxial divisional oculomotor paresis suggests intraaxial fascicular organization. *Ann Neurol.* 1990;28:589-590.

Marchiafava-Bignami Disease, Syndrome of Interhemispheric Disconnection, and Right-handed Agraphia in a Left-hander

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• We present an original case of Marchiafava-Bignami disease in a 47-year-old left-handed alcoholic man. Computed tomography and magnetic resonance imaging demonstrated the typical lesion, a necrosis of the middle portion of the corpus callosum. Diagnosis may thus be established in the living. In our case, the course was not fatal, which, to our knowledge, has only been described in four other cases in the literature. Clinically, our patient demonstrated an interhemispheric disconnection syndrome. The striking feature is that some of the symptoms were on the side opposite of the one that has previously been described in the literature, eg, right-handed agraphia, while others were on the usual side, eg, left-handed anomia. We discuss cerebral dominance for speech and handedness in left-handers and come to the conclusion that our patient's clinical features can only be explained by right hemispheric dominance for handedness and bilateral hemispheric representation of speech.

(*Arch Neurol.* 1991;48:986-988)

Marchiafava-Bignami disease is an uncommon disorder associated with alcoholism, presumably of nutritional or metabolic origin. This disease is defined by its pathologic features, ie, a symmetrical demyelination of the middle portion of the corpus callosum, with or without necrosis. The clinical features of the disease are quite variable, and diagnosis was rarely made before postmortem examination until computed tomography and magnetic resonance imaging were introduced. In some cases, the diagnosis is suggested by a syndrome of interhemispheric disconnection.[1-4] The course of the disease is usually fatal, yet we found four cases of recovery in the literature.[3-6]

We report the case of a left-handed alcoholic patient with Marchiafava-Bignami disease. The patient recovered, and special testing revealed an interhemispheric disconnection syndrome characterized by right-handed agraphia and apraxia, a sign of the foreign hand on the right side, and left-handed anomia.

REPORT OF A CASE

A 54-year-old left-handed male alcoholic was found unconscious at his home and was admitted to the hospital. Since his wife had left home 8 weeks previously, he had eaten very little but had continued drinking. General physical examination revealed malnutrition. The patient was confused and disoriented as to time and space. Neurologic examination revealed ataxia and gegenhalten. The ankle reflexes were abolished. There was no motor or sensory deficit. Plantar reflexes were flexor. No ocular motor disturbances were noted. The results of routine laboratory tests were normal. A cranial computed tomographic scan with and without contrast medium showed abnormal hypodensity of the corpus callosum, extending from the genu to the splenium; there was no contrast enhancement. The patient received thiamine treatment, and within a week he had partially recovered: consciousness was normal, and the ataxia and gegenhalten had disappeared. Cranial magnetic resonance imaging was performed on day 15 (Fig 1). A low-signal intensity area was demonstrated in the corpus callosum, extending from the genu to the splenium in T_1-weighted images. In T_2-weighted images, the abnormal area was demonstrated as a high-intensity area, which extended beyond the corpus callosum into the hemispheric white substance of the frontal horns. Neuropsychological testing was performed; then the patient was transferred to a convalescence ward. Six months later, a second series of neuropsychological tests were performed. A detailed account of his cognitive deficits is given below. A new computed tomographic scan showed the same abnormalities. Cerebral blood flow studies were performed with technetium Tc 99m exametazime and the scintillation camera. Several areas of decreased perfusion were demonstrated: the posterior zone of the frontal lobe and the parietal lobe of the right hemisphere; the temporo-occipital area of the left hemisphere; and the right cerebellum hemisphere with cerebellum diaschisis.

NEUROPSYCHOLOGICAL FINDINGS

The patient was tested once he had recovered normal consciousness. The results were as follows:

1. Spontaneous speech was intact. Comprehension of verbal or written material was good. When asked to write, under dictation, spontaneously, or copying, the patient performed well with his left hand, but was unable to draw letters or words with his right hand (apraxic agraphia) (Fig 2). Drawing geometric figures was disturbed with both the left and the right hands (constructional apraxia).

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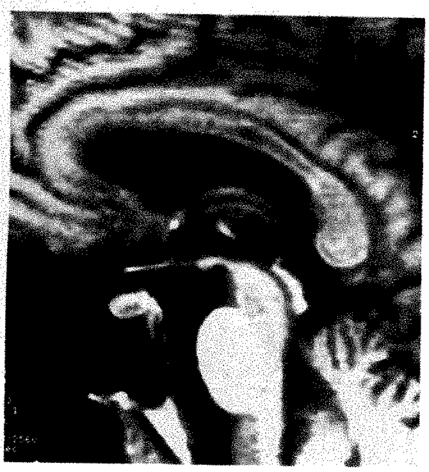

Fig 1.—Cranial magnetic resonance imaging scan. There was a low-signal intensity area in the corpus callosum in T_1-weighted images.

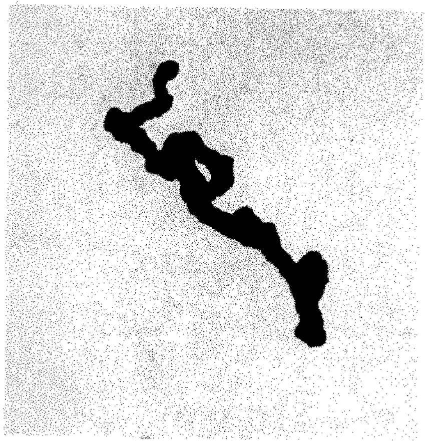

Fig 2.—Apraxic agraphia of the right hand. Writing under dictation: letter *b*.

2. Objects placed in the patient's right hand with his eyes closed were easily named. In the left hand, objects were not identified or with much delay, yet the patient could pick them out among others presented to him. In the same fashion, objects were named when presented in the right visual field, but not in the left. In the left visual field, the patient would deny seeing anything, yet he could correctly identify the objects among others.

3. Cooperation between the patient's left and right hands was disturbed, and the patient demonstrated diagnostic dyspraxia with an "alien" right hand. For instance, a scene observed during breakfast: if the right hand grasps a slice of bread, the patient is unable to release it, and when the left hand tries to take it from the right hand, there is an opposite movement of avoidance.

4. When asked to perform commands, the patient was disinclined to use his right hand, and when he did, responses were delayed. There was desynchronization of bilateral symmetrical movements, such as clapping hands together and on the lap.

5. As for performing to verbal command, responses were delayed or incorrect with right hand, although intent was good. The left hand performed well. Imitation was well done with both hands.

Six months later in follow-up, neuropsychological testing confirmed apraxic agraphia without aphasia in the right hand and bilateral constructional apraxia, which predominated in the right hand. There was persisting anomia (tactile aphasia) of the left hand. Tachistoscopy studies confirmed extinction of the left visual field. Dichotic testing revealed extinction of the left ear as well. Diagnostic dyspraxia and the right "alien hand" persisted. Crossed motor activities were impossible to perform, while imitation of ipsilateral activities was correct. There was right-hand ideomotor apraxia with neglect of the right hand.

COMMENT

The diagnosis of Marchiafava-Bignami disease in our patient was established on the association of a history of severe alcoholism, a clinical syndrome of interhemispheric disconnection, and neuroradiological images of extensive necrosis of the corpus callosum.

Course and Prognosis

Our patient did not die of Marchiafava-Bignami disease. Such a favorable clinical course is uncommon. We found four cases in the literature with a similar clinical course.[3-6]

Delangre et al[4] suggested that patients who survived had incomplete lesions with relative sparing of the superior commissure fibers, whereas lesions extending into the convolution white matter brought about death or severe dementia. This hypothesis was not confirmed by our case, in which magnetic resonance imaging demonstrated lesions that extended about the frontal horns and yet the clinical course was favorable.

Syndrome of Interhemispheric Disconnection and Agraphia

Bykov and Speransky[7] and Myers[8] demonstrated that corpus callosum is necessary for interhemispheric transfer of information in animals. The clinical aspects of postcallosotomy patients have been studied by Gazzaniga et al,[9] Geschwind and Kaplan,[10] and Bogen and Bogen[11], who showed that in animals and man, after section of the corpus callosum, the two isolated half brains behave independently, and that transfer of information is no longer possible between them.

Liepmann and Maas[12] were the first to point out that unilateral apraxia and agraphia in the absence of aphasia could be the signs of interhemispheric disconnection. This was confirmed by the studies of Gazzaniga et al[9] and Geschwind and Kaplan.[10] However, in these previous cases, agraphia and apraxia existed in the left hand, not in the right hand. In our case, agraphia and apraxia occurred in the right hand.

From a neuropsychological point of view, we found only four cases of right-handed agraphia without aphasia in the literature that could be explained by a interhemispheric disconnection. Unlike these four cases, our patient's lesion was limited to the corpus callosum.

Dejerine and Thomas[13] reported the case of a 49-year-old woman, left-handed except for writing, who presented with left hemiplegia and aphasia. By the end of her illness, 5 years later, she had recovered speech, and she had left hemiplegia with agraphia in the intact right hand. At postmortem, the brain showed no lesion in the left hemisphere, but a massive infarction was seen involving the right hemisphere and destroying the right side of the corpus callosum. In this case, there was agraphia in the hand opposite of an intact left hemisphere, which was capable of other language activities associated with a lesion of the right side of the corpus callosum.

The case of Nielsen[14] involved a left-handed man who wrote with his right hand. The patient abruptly developed weakness of his right leg and lost the ability to write with his right hand. Writing was still possible with his left hand. The clinical features suggest stroke in the anterior cerebral artery territory with lesions of the anterior four fifths of the corpus callosum.[15]

The patient of Botez and Crighel[16] was a 55-year-old woman. She was ambidextrous but wrote with the right hand, and her sister was left-handed. Embolism of the left middle cerebral artery caused receptive aphasia in this patient. After a rapid recovery, she developed a partial syndrome of interhemispheric disconnection consisting of writing disorders and tactile aphasia of the right hand, without agraphia of the left hand or aphasia. The evidence in this case suggested to the authors that their patient's representation of speech was bilateral and that of her writing was right hemispheric.

Heilman et al[15] described a left-handed 62-year-old man who developed a left hemiplegia without aphasia or alexia, and who lost ability to write with his right hand. He was right-handed for writing and one of his brothers was left-handed. He also showed severe right apraxia and extinction of the left side on testing with simultaneous auditory, somesthetic, and visual stimuli. These symptoms suggested a partial syndrome of interhemispheric disconnection. Analysis of this case suggested to the authors the presence of language dominance in the left hemisphere and dominance for handedness in the right one.

Another particularity in the interhemispheric disconnection syndrome of our patient is that the "sign of the foreign hand" affected the right side, not the left. This sign was described by Brion and Jedynak[17]: the patient complains that his hand does not obey and has difficulties recognizing his hand as being his own. When both hands are held behind his back, "the patient is unable to tell who the hand belongs to although he is perfectly aware of the presence of another hand in his own." This sign is not constantly present in the syndrome of interhemispheric disconnection, but when it exists, it is very important for diagnosis. It has been described on the left side or bilaterally. In our case, the sign affected the right side only, which, we believe, has not previously been described in the literature.

Cerebral Dominance

Several authors have studied the problem of cerebral dominance. Botez[18] distinguished three types: (1) an absolute cerebral dominance of the left hemisphere in right-handed subjects without family history of left-handedness; (2) a bilateral cerebral dominance in right-handed subjects with familial left-handedness, in left-handed subjects, and in ambidextrous subjects; and (3) a dissociated cerebral dominance in some subjects who have one of the speech functions located in one hemisphere and the remaining functions in the other.

Liepmann[19] suggested that manual dominance reflects the ability of one hemisphere to learn motor tasks more promptly than the other. According to this hypothesis, in some people, language dominance could be in one hemisphere and dominance of handedness in the other.

In their study of agraphia and apraxia in a left-hander, Heilman et al[15] suggested that a left-hander who is right-brain dominant for motor control may be either right brained or left brained for speech dominance. If a patient is right brained for both complex motor sequence learning and speech, and writes with the right hand, a callosal lesion should produce right-sided agraphia and apraxia but no left-sided agraphia; if the patient is right brained for handedness and left brained for speech, and writes with the right hand, a callosal lesion should produce bilateral agraphia, apraxic agraphia in the right hand, and aphasic agraphia with ideomotor apraxia in the left hand. They added that their conclusions would be modified if, after the callosal lesion, the patient could shift to the other hemisphere for speech or motor control.

In our case, left-handed anomia and extinction of audition of the left ear suggest left hemisphere dominance for speech, while apraxic agraphia and ideomotor apraxia predominating on the right side suggest right hemisphere dominance for handedness. The fact that, instead of bilateral agraphia, our patient showed only apraxic agraphia of the right hand can be explained by two hypotheses: either there was transfer of dominance from one hemisphere to the other after the onset of the callosal lesion, as suggested by Heilman et al,[15] or the patient had bilateral cerebral dominance for language functions from the start, as suggested by Botez and Crighel.[16] We believe that the second hypothesis best explains the clinical features.

Analysis of the left-handed anomia in our patient suggests that the right parietal lobe had no functional connection with the area of representation of speech in the right hemisphere, but was exclusively dependent of the area of representation of speech in the left hemisphere for naming objects placed in the left hand. Finally, it is interesting to note that the cerebral blood flow studies demonstrated decreased perfusion of the posterior zone of the frontal and parietal lobes of the right hemisphere and of the temporo-occipital area of the left hemisphere. These areas are considered to be possible representations of language functions. According to Nielsen,[14] lesions of the posterior part of the middle frontal gyrus (Hexner's area) or lesions of the angular gyrus can bring about agraphia. This author considered these zones to be the area of memorization of the writing movements and the area of visualization of written language, respectively, and believed that coordination of these two areas is necessary for the execution of writing movements.

According to Hrbek,[20] representation of the writing muscles' motor control is situated in the posterior part of the middle frontal gyrus, and that of the act of writing itself (praxia) is in the parietal lobe: lesions of these zones could produce agraphia. In our case, neuroradiological investigations showed no lesion in these part of the hemispheres. Decreased blood flow may be considered as a sign of decreased activity, which could be an indirect sign of the disconnection.

The second series of neuropsychological tests performed in this study were administered by P. Bachkine, MD, Hôpital La Pitié-Salpêtrière, Paris, France.

References

1. Lechevalier B, Andersson JC, Morin P. Hemispheric disconnection syndrome with a 'crossed avoiding' reaction in a case of Marchiafava-Bignami disease. *J Neurosurg Psychiatry.* 1977;40:484-497.
2. Lhermitte F, Marteau R, Serdaru M, Chedru F. Signs of interhemispheric disconnection in Marchiafava-Bignami disease. *Arch Neurol.* 1977:34:254.
3. Barbizet J, Degos JD, Lejeune A, Leroy A. Syndrome de dysconnection inter-hémisphèrique avec dyspraxie diagonistique au cours d'une maladie de Marchiafava-Bignami. *Rev Neurol (Paris).* 1978;134:781-789.
4. Delangre T, Hannequin D, Clavier E, Denis P, Mihout B, Sanson M. Maladie de Marchiafava-Bignami d'évolution favorable. *Rev Neurol (Paris).* 1986;142:933-936.
5. Leventhal CM, Baringer JR, Arnajon BG, Fisher CM. A case of Marchiafava-Bignami disease with clinical recovery. *Trans Am Neurol Assoc.* 1965;90:987-991.
6. Kawamura M, Shiota J, Yagishita T, Hirayama K. Marchiafava-Bignami disease: computed tomographic scan and magentic resonance imaging. *Ann Neurol.* 1985;18:103-104.
7. Bykov KM, Speransky AD. Observation upon dogs after section of the corpus callosum. *Coll Papers Physiol Lab Pavlov.* 1924;1:47-59.
8. Myers RE. Function of corpus callosum in interocular transfer. *Brain.* 1956;79:358-363.
9. Gazzaniga MS, Bogen JE, Sperry RW. Some functional effects of sectioning the cerebral commissures in man. *Proc Natl Acad Sci.* 1962;48:1765-1769.
10. Geschwind N, Kaplan E. A human cerebral deconnection syndrome. *Neurology (Minneap).* 1962;12:675-685.
11. Bogen JE, Bogen GM. The other side of the brain, III: the corpus callosum and creativity. *Bull L A Neurol Soc.* 1969;34:191-220.
12. Liepmann H, Maas O. Fall von linksseitiger Agraphie und Apraxie bei rechtsseitiger Lähmung. *J Psychol Neurol.* 1907;10:214-230.
13. Dejerine J, Thomas A. Contribution à l'étude de l'agraphie chez les gauchers. *Rev Neurol.* 1912;24:213-226.
14. Nielsen JM. *Agnosia, Apraxia, Aphasia: Their Value in Cerebral Localization.* 2nd ed. New York, NY: PB Hoeber; 1946:37-46, 186-188.
15. Heilman KM, Coyle JM, Gonyea EF, Geschwind N. Apraxia and agraphia in a left-hander. *Brain.* 1973;96:21-28.
16. Botez MI, Crighel E. Partial disconnection syndrome in an ambidextrous patient. *Brain.* 1971;94:487-494.
17. Brion S, Jedynak CP. Troubles du transfert interhemisphérique (callosal disconnection): à propos de 3 observations de tumeurs du corps calleux: le signe de la main étrangère. *Rev Neurol (Paris).* 1972;126:257-266.
18. Botez MI. *Afazia si sindroamele corelate in procesele expansive intracraniene.* Bucharest, Romania: Bucuresti Akademiai; 1962.
19. Liepmann H. Die linke Hemisphäre und das Handeln. In: Drei Aufsätze aus dem Apraxiegebiet. Berlin, Germany: S Karger; 1908:17-50.
20. Hrbek J. Afasie, agrafie, alexie, apraxie, agnosie. Novy vyklad na zaklade uceni. *Acta Univ Palac Olom.* 1955:11-24.

Classified Advertising

All classified advertising orders, correspondence and payments should be directed to: Archives of Neurology, P.O. Box 1510, Clearwater, Florida 34617. Our telephone numbers are: 800-237-9851; 813-443-7666. Please do not send classified ads, payments or related correspondence to the AMA headquarters in Chicago. This causes needless delay.

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Professional Opportunities

KANSAS — Board-certified, board-eligible neurologist to join child neurologist in rebuilding a three-person practice in the largest city in Kansas. Three large, well-equipped hospitals available for resident and undergraduate medical education. Located in clean, progressive community described as the franchise capital of the country. Competitive salary and benefits available. Send CV to: Richard C. Gilmartin, MD, 2620 East Central, Wichita, KS 67214.

MAUI ORTHOPEDIC and Sports Medicine seeks neurologist to establish independent practice. Contact: William Gfeller, 450 Hookahi Street, Wailuku, Maui, HI 96793. (808) 244-5541.

SOUTHEAST COAST — Pediatric Neurologist: Excellent quality of life available in Savannah-Hilton Head Area, site of the 1996 Olympic Games sailing events. Outstanding recreational opportunities, nation's largest urban Historic District, and superb symphony are among the attractions of living here. A well-trained, personable neurologist with special competence in child neurology is needed for a busy practice, currently consisting of two adult neurologists and one neurologist doing adult and child neurology, all with strong academic backgrounds. CT, EEG, EMG and physical therapy are available in-office with large hospital practice available in three hospitals, including a major regional teaching hospital, affiliated with the Medical College of Georgia. First year guarantee is $80,000 plus bonus, leading to full partnership after two years. Earnings potential, availability of strong multi-specialty support, and opportunities for teaching are extraordinary. If interested contact: Randy Wellman, Office Manager, Savannah Neurological Associates, PC, P.O. Box 23059, Savannah, GA 31403. (912) 354-8151.

ADULT NEUROLOGIST to associate with two separate, busy solo neurologists. Practices are referral based, with two separate offices and three voluntary hospitals. Successful candidate would be expected to develop a separate solo, but collaborative practice. Established physicians would expect to provide substantial support for beginning physician. Opportunity would provide for cross coverage and joint venturing of facilities. Successful candidate should have excellent clinical skills. The medical community has excellent neurophysiology, neuroradiology, and neurosurgery. Located in a medium size city with both excellent living conditions and an extremely solid economic base. Please contact: Jeffrey A. Ribner, MD, 503 Plaza Drive, Vestal, NY 13850. (607) 729-1521 or Robert R. Taylor, Jr., MD, 269 Riverside Drive, Johnson City, NY 13790. (607) 798-7143.

NEUROLOGIST BC/BE — Washington, DC metropolitan area sought by busy four person group. We seek a personable, energetic clinician with competence in EEG, EMG, EP. Other subspecialty expertise welcomed. Respond with CV to: Larry Einbinder, MD, 8200 Wisconsin Avenue, Bethesda, MD 20814.

CAROLINA — PIEDMONT: BC/BE adult neurologist to join two neurologists in busy clinical practice. All neurodiagnostics available. Salary leading to partnership. Position available immediately. Send CV to: Marilyn Miller, 145 Dillon Drive, Spartanburg, SC 29302.

MELBOURNE, FLORIDA — Outstanding opportunity for an adult neurologist who would like to join a group of nine neurologists. Our group includes child neurologist, neuromuscular specialists and neurorehabilitation specialists. We live in a beautiful, high tech, beachside community with great schools and affordable housing. Please send CV to: Search Committee, P.O. Box 693, Melbourne, FL 32902.

Professional Opportunities

CLINICAL NEUROLOGIST — The Division of Neurology at The Mary Imogene Bassett Hospital is seeking a fourth neurologist in the practice of pediatric and adult neurology. The candidate must be BE/BC and interested in teaching. The Bassett Hospital is a multi-specialty group practice which provides primary and tertiary care to a ten-county rural region of Upstate New York, and is a major teaching affiliate of Columbia University. Members of the Division of Neurology hold faculty appointments at Columbia and Darmouth medical schools. The area combines environmental, recreational, and cultural advantages with excellent schools. We offer a competitive salary, faculty appointment, and liberal fringe benefits. Please send CV and correspondence to: Mary Anne Whelan, MD, Division of Neurology, The Mary Imogene Bassett Hospital, One Atwell Road, Cooperstown, NY 13326. (607) 547-3240.

METROPOLITAN WASHINGTON, DC AREA

Rapidly expanding neurology practice, with multiple locations, is seeking a BE/BC neurologist to join our dynamic team. Our offices are conveniently located, providing easy access to the areas finest hospitals as well as the nation's capital. We offer a competitive salary, excellent benefits and the opportunity for partnership. For more information please call or write:

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10721 Main Street, Suite 2500
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NEUROLOGIST — Beautiful Durango, Colorado is recruiting a BC/BE neurologist: Mercy Medical Center is an extremely progressive and active 100-bed facility and is doing well financially and growing — primarily due to an excellent staff of 90 physicians and a decent economy. Durango is located in southwestern Colorado, with an abundance of outdoor recreation (skiing, fishing, hunting, bicycling) excellent restaurants, an excellent local 4-year college, great weather and excellent schools! For more informaion about this excellent practice opportunity, mail CV or call: Bob Conrad, Vice President, Mercy Medical Center, 375 East Park Avenue, Durango, CO 81301. (303) 247-3804.

INDIANAPOLIS METROPOLITAN AREA: Young and aggressive Indianapolis neurological group seeks board-eligible or -certified associate. Broad spectrum of clinical experience is important. Experience in EEG, evoked potentials and EMG is necessary. Sub-specialty training is desirable, but not necessary. Indianapolis is a desirable, growing, clean and safe community. Excellent salary plus bonus and beneifts leading to partnership opportunity. Send CV to: Midwest Neurological Insitute, 998 East Main Street #202, Danville, IN 46122.

CHICAGO SUBURBAN solo practitioner with a busy practice seeking a full-time BC/BE clinical neurologist. EMG skills required. Immediate opening. Wonderful opportunity to expand with possible early partnership. Reply with CV to: Yvonne Jurcik, MD, 125 East Lake Cook Road, Buffalo Grove, IL 60089.

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Professional Opportunities

EXCELLENT OPPORTUNITY for BC/BE neurologist to join 80-physician comprehensive, multispecialty group in San Francisco Bay Area. Large, varied referral base from Pediatrics, IM, FP, and Surgery. EMG/NCV, EEG, Evoked Response Testing, CT, MRI, Radiology support all available on site. Opportunity to interface with specialists of all types including neurosurgeons. Major university teaching affiliation encouraged and possible. Close proximity to 400-bed full service, modern hospital serving population of 300,000. Competitive guaranteed salary with bonus productivity plan for initial 18 months leading to partnership track. Extensive benefit package including housing incentives. Unique cultural, recreational and educational opportunities. Send CV to: Gary D. Zweig, MD, Recruitment Chairman, Sunnyvale Medical Clinic, P.O. Box 3496, Sunnyvale, CA 94088-3496.

OCHSNER NEUROLOGIST — The Ochsner Clinic of Baton Rouge seeks qualified neurologists to expand its department in our multi-specialty regional clinic. The practice offers an opportunity to practice in a setting which supports innovation and involvement in education and research. Competitive salary and excellent fringe benefits program. Send CV to: Ochsner Clinic of Baton Rouge, Physician Recruiting Support Services, 16777 Medical Center Drive, Baton Rouge, LA 70816; or call: (800) 488-2240.

NEUROLOGIST: Urban area in North Carolina. BC/BE, to join solo neurologist in a rapidly expanding, progressive and active practice. All neurodiagnostic modalities available. Excellent salary leading to partnership. Experience in EMG, EEG and EPs. Please reply with CV to: Box #822, c/o AON.

EXCELLENT OPPORTUNITY for BC/BE neurologist to practice in large eastern metropolitan area. Opening for July 1992 or earlier, for private practice with geographic full-time appointment at large teaching institution. Medical school appointment, teaching and research opportunities. Subspecialty in movement disorders, muscle diseases or neuro-oncology preferred but not required. Submit CV to: P.O. Box 5849, Pittsburgh, PA 15209-0849.

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BC/BE NEUROLOGIST — Exceptional opportunity to establish a practice in northwest Denver suburb. No investment required. Strong referral base. Opportunity to affiliate with two busy neurologists with office located adjacent to beautiful 400-bed hospital with state-of-the-art technology. Excellent opportunity for subspecialty trained with a strong interest in the clinical care of patients. Send CV to: Box #819, c/o AON.

NEUROLOGIST — The Cleveland VA Medical Center is recruiting for a part-time (5/8) position for a neurologist. The applicant must be board-certified or board-eligible in neurology, have expertise in both EMG and EEG and satisfy requirements for appointment in the Neurology Department at Case Western Reserve University. Responsibilities include attending neurology outpatient clinics in Youngstown, Canton, Brecksville, and Cleveland, Ohio, in addition to his/her responsibility for inpatient, consult services, reading EEGs and performing EMGs. Interested individuals should contact: Thomas R. Claflin at (216) 526-3030, Extension 7916. Or send a resume to his attention: Personnel Service 05(B), VAMC, 10000 Brecksville Road, Brecksville, OH 44141. The Cleveland VAMC is proud to be an equal employment opportunity employer.

SOUTHERN COLORADO — Exceptional practice and area. Opportunity to work with highly respected neurologist within a multi-specialty group. Practice to include: adult neurology, EEG, EMG, evoke potentials, CT and MRI. This vibrant community of 150,000 is located along the front range of the beautiful Rocky Mountains providing for a lifestyle second to none. Highly competitive first year income plus comprehensive benefits and relocation followed by partnership offering. For further details reply to: Wendy Perlman, 9360 Sunset Drive, Suite 250, Miami, FL 33173. Or call: (800) 368-2416, Extension 118.

CHARLOTTE, NORTH CAROLINA: High quality group of five neurologists, all of whom are subspecialized, seeks to add a well-trained specialist. Contact: Mike Kaufman, MD, 1900 Randolph Road, Suite 1010, Charlotte, NC 28207. Or call: (704) 334-7311.

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NEUROLOGIST — BC/BE to join main branch of thirty-five physician multi-specialty group. Excellent clinic and hospital facilities. Very competitive salary and benefit package. Excellent opportunity. Good hunting, fishing. Good schools, a beautiful place to raise a family. Call Executive Administrator collect (701) 857-0236, or write: Medical Arts Clinic, PC, P.O. Box 1489, Minot, ND 58702-1489.

SOUTHERN CALIFORNIA

Outstanding opportunity for motivated BC/BE neurologist with clinical and electrodiagnostic proficiency. Join a solo neurologist in an established and respected office and hospital-based practice. Balanced private/PPO/HMO profile. Excellent growth prospects.

New office with fully equipped eletrodiagnostic laboratory located in North Orange County. Area offers attractive living conditions, recreational opportunities and excellent public schools.

Generous guaranteed salary and benefit package with opportunity for early partnership.

Box 821, c/o AON

DURANGO, COLORADO: Need BC/BE neurologist to join neurosurgeon in southwest Colorado. Near 94 acute plus 11 skilled nursing bed hospital (Mercy Medical Center). 140,000 catchment area. No neurologist now based in Durango. Sole neurosurgeon presently in private practice, Medical Director Pain Rehabilitation Center, plus directs neurodiagnostic lab (EEG, EMG, NCV, evoked potentials, brain mapping, thermogram). Needs help! Great place to live — hiking, fishing, hunting, etc. Will split practice with right applicant. Spouse must be willing to live in small town rural area. Mail CV or call: Ben Crue, Jr, MD, FACS, 1130 Main Avenue, Durango, CO 81301. (303) 259-0779.

Positions Available

NEW ENGLAND SEACOAST COMMUNITY seeks second neurologist for community hospital practice. Excellent location with abundant outdoor recreation, good schools, major scientific institutions nearby. First year salary with early partnership option. Please contact: Michael Leahy, MD, 12 Bramblebush Park, Falmouth, MA 02540.

SOUTHERN CALIFORNIA — BC/BE clinician to join busy solo neurologist covering 320-bed hospital, complete neurodiagnostic laboratory and surrounding community. Contact: Thomas Di Julio, MD, 1703 Termino Avenue, Suite 208, Long Beach, CA 90274.

NEUROLOGIST: BC/BE. Must have skills in EEG, EMG and evoked potentials. To be associated with two neurologists in private practice, in a medical center location, with a expanding modern 181-bed hospital with complete modern equipment, and all specialties are represented. Situated in an attractive high desert area of the northwest with abundant recreational activities including the finest skiing, hiking, hunting, and fishing. Excellent schools available, both public and private. This is a very active practice in a drawing area of 175,000 and an excellent opportunity. Reply with curriculum vitae to: Box #823, c/o AON.

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Fellowships

PEDIATRIC MOVEMENT Disorder Fellowships: Fellowship available in basic or clinical aspect of pediatric movement disorder for one or two years. Starting date is July 1, 1991. Candidates should have completed a neurology residency. This program stresses the neuropharmacology of movement disorders. Fellow will participate in federally sponsored clinical drug trials with a Research Nurse Practitioner in active outpatient and inpatient setting. For information contact: Dr. Michael R. Pranzatelli, Director, The National Pediatric Myoclonus Center, Neurology Department, Children's National Medical Center, 111 Michigan Avenue, NW, Washington, DC 20010. (202) 745-2120.

FELLOWSHIP IN CEREBROVASCULAR disease: Fellowships in cerebrovascular disease are available in the Department of Neurology at the University of Iowa. Comprehensive clinical training in diagnosis and management of patients with stroke is complemented by opportunities for clinical or basic research. Fellows are active participants in patient care and collaborate in several on-going local and multi-center clinical research studies. Candidates should be board-eligible or -certified in neurology and licensed to practice medicine in the United States. Please send inquiries to: Harold P. Adams, Jr, MD, Division of Cerebrovascular Diseases, Department of Neurology, University of Iowa, Iowa City, IA 52242; or call: (319) 356-4110. The University of Iowa is an affirmative action, equal opportunity employer. Women, minorities, and handicapped are encouraged to apply.

NATIONAL STROKE ASSOCIATION announces career-development fellowship awards ($30,000/year) for stroke research. Application due January 15, 1992 for July 1992 commencement. Contact: National Stroke Association, 300 East Hampden Avenue, #240, Englewood, CO 80110. (303) 762-9922.

PAIN FELLOWSHIP — The Pain Service in the Department of Neurology at Memorial Sloan-Kettering Cancer Center is seeking a board-eligible/board-certified neurologist for a pain fellowship. This is a one or two year position which offers comprehensive training in pain evaluation and treatment with a strong emphasis on cancer pain. Fellows will participate in clinical investigations of neuro-oncologic pain syndromes and the pharmacology of opioid analgesics. Laboratory research opportunities directed at the mechanisms of opiate action and the molecular pharmacology of opiate receptors are also available. Please contact: Kathleen M. Foley, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

FELLOWSHIP IN EEG available immediately at combined VA hospital, Delaware/Thomas Jefferson University Program. Candidates with completed neurology residency. Contact: Leonard Katz, MD, VA Medical Center, Wilmington, DE 19805. (302) 994-2511.

MULTI-DISCIPLINARY FELLOWSHIP in pain medicine is being offered for July 1, 1992. Two-to-three year position is available with rotations in neurosurgery, neurology, oncology, anesthesia, and psychiatry. Clinical and basic science research projects will also be offered. Interested persons should submit inquiries and CV to: James Campbell, MD, Professor of Neurosurgery, c/o Kathleen Wiley, Pain Treatment Center, Johns Hopkins Hospital, Meyer 1-130, 600 North Wolfe Street, Baltimore, MD 21205.

Faculty Positions

ACADEMIC NEUROLOGIST sought with fellowship training in neuromuscular diseases and EMG. Opportunity to develop research program, teach neurology residents, and start a fellowship. State-of-the-art equipment and technician furnished. Nerve and muscle biopsy laboratory available in the department. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

Faculty Positions

ACADEMIC NEUROLOGIST sought with competence in sleep disorders to direct sleep center. Opportunity also in epilepsy, EEG, and evoked potentials, teach neurology residents and students. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

ACADEMIC NEUROLOGIST sought with training in cerebrovascular disease to develop program. Collaborate with neuropathology and radiology to develop research. Teach neurology residents. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

NEUROBIOLOGY/CLINICAL faculty positions — The Sanders-Brown Center on Aging at the University of Kentucky invites applications for two tenure-track faculty appointments at the Assistant Professor level from board-eligible/-certified neurologists or psychiatrists with basic neuroscience or clinical research interests in Alzheimer's disease. The successful candidates will have faculty appointments in the appropriate academic departments of the College of Medicine. The appointees will be expected to develop their own research programs, be willing to participate in multi-disciplinary Alzheimer's disease research and have some clinical responsibilities primarily related to dementing illnesses. Excellent start-up packages are available. The Sanders-Brown Center is one of the NIA-funded Alzheimer Disease Research Centers and has a separate 40,000 square foot building with excellent laboratory facilities. A letter of interest, a recent curriculum vitae and names of three references should be submitted to: William R. Markesbery, MD, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY 40536. (606) 233-6040. The University of Kentucky is an equal opportunity employer.

Associate Professor of Neurology/ Neuro-Oncology

The Department of Neurology at Temple University School of medicine seeks a Neuro-oncologist at the Associate Professor level to direct the clinical Neuro-oncology program at the Temple University Comprehensive Cancer Center. The program will provide comprehensive care for patients with primary and secondary CNS malignancy, indirect effects of systemic cancer and cancer pain. Facilities and support are available for the development of a clinical research program and collaborative opportunities are available in the area of molecular biology of brain tumors. Candidates should be board certified/board eligible in Neurology with additional fellowship training in Neuro-oncology. Applications should be forwarded to **Jeffrey I. Greenstein, M.D., Chair, Department of Neurology, Temple University School of Medicine, 3401 N. Broad Street, Philadelphia, PA 19140.** Temple University is an Equal Opportunity/Affirmative Action Employer.

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ACADEMIC NEUROLOGIST — The Department of Neurology at Francis Scott Key Medical Center, a Johns Hopkins Medical Institution, seeks an academically-oriented adult BC/BE neurologist with expertise in EMG and NCV to run EMG Lab. Interest in neuromuscular assessment and research needed. Fellowship in EMG/NCV required with BC/BE in EMG (AAEM). The appointment will be full-time, at the Assistant Professor level, and will include responsibilities in research, clinical teaching, and patient care. Interested candidates should send a CV and three letters of reference to: Peter W. Kaplan, MD, Johns Hopkins School of Medicine, Francis Scott Key Medical Center, 4940 Eastern Avenue, Baltimore, MD 21224.

ACADEMIC NEUROLOGIST: A full-time academic position is available at the Assistant Professor level at Vanderbilt University Medical Center. Candidates should be board-certified/board-eligible in neurology and should have completed two years of full-time fellowship in epilepsy and clinical neurophysiology. The position includes teaching responsibilities and research. The preferred candidate will have experience in clinical epilepsy, long-term monitoring, electrocorticography, and experimental drug studies. Interested individuals should send CV to: Bassel Abou-Khalil, MD, Department of Neurology, Vanderbilt University Medical Center, 2100 Pierce Avenue, Room 336, Nashville, TN 37212.

Residencies

ADULT NEUROLOGY RESIDENCY PGY-IV position available at the University of Colorado School of Medicine for July, 1991. Contact: James P. Kelly, MA, MD, Director of Resident Selection, Department of Neurology, UCHSC B-183, 4200 East Ninth Avenue, Denver, CO 80262. (303) 270-8760.

NEUROLOGY RESIDENCY PROGRAM at the University of North Carolina. PGYII position available for entrance into Neurology Residency Program for 1992. Appointment will be made through the Neurology Residency Matching Program in 1992. Our program offers strong clinical training in general adult and child neurology as well as subspeciality exposure to epilepsy, sleep disorders, neuromuscular diseases and pain. For information contact: John A. Messenheimer, MD, School of Medicine, Department of Neurology, University of North Carolina, CB #7025, 751 Clinical Sciences Building, Chapel Hill, NC 27599-7025. (919) 966-3707.

THE UNIVERSITY OF Cincinnati Neurology Department is offering a second year neurology residency position (PGY III) beginning as soon as possible. For information contact: Joseph P. Broderick, MD, Residency Director, Department of Neurology, University of Cincinnati Medical Center, Cincinnati, OH 45267-0525. (513) 558-5431.

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Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

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WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

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Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

Dilantin® Kapseals®
(extended phenytoin sodium capsules, USP)

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been reported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to phenytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. Appropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and absence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversible cerebell dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recommended. Do reduction of phenytoin therapy is indicated if plasma levels are excessive; if symptoms persi termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the importance adhering strictly to the prescribed dosage regimen, and of informing the physician of any clinic condition in which it is not possible to take the drug orally as prescribed, eg, surgery, etc.

Patients should also be cautioned on the use of other drugs or alcoholic beverages without fi seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to minimize t development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to achieve optim dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease phenytoin levels which phenytoin may affect. Serum level determinations for phenytoin are especially helpf when possible drug interactions are suspected. The most commonly occurring drug interactio are listed below: 1. Drugs which may increase phenytoin serum levels include: acute alcoh intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol, disulfira estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phenothiazine phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodone.

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic alcohol abus reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains calcium io which interfere with the absorption of phenytoin. Ingestion times of phenytoin and antac preparations containing calcium should be staggered in patients with low serum phenytoin leve to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: phenobarbit sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarbital, valpro acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitate seizures susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired by phenyto include: corticosteroids, coumarin anticoagulant digitoxin, doxycycline, estrogens, furosemide, or contraceptives, quinidine, rifampin, theophyllin vitamin D.

Drug/Laboratory Test Interactions: Phenytoin m cause decreased serum levels of protein-bound iodi (PBI). It may also produce lower than normal values f dexamethasone or metyrapone tests. Phenytoin m cause increased serum levels of glucose, alkaline pho phatase, and gamma glutamyl transpeptidase (GGT

Carcinogenesis: See "Warnings" section for inform tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this drug becaus phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations encountere with phenytoin therapy are referable to this system and are usually dose-related. These inclu nystagmus, ataxia, slurred speech, decreased coordination and mental confusion. Dizzines insomnia, transient nervousness, motor twitchings, and headaches have also been observed. The have also been rare reports of phenytoin induced dyskinesias, including chorea, dystonia, trem and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patients receivin long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver damage.

Integumentary System: Dermatological manifestations sometimes accompanied by fever hav included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) is the mo common; other types of dermatitis are seen more rarely. Other more serious forms which ma be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosus, Stevens Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally been reporte in association with administration of phenytoin. These have included thrombocytopenia, leuk penia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone marrow sup pression. While macrocytosis and megaloblastic anemia have occurred, these conditions usuall respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperplasia, pse dolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warnings).

Connective Tissue System: Coarsening of the facial features, enlargement of the lips, gingiv hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to, symptom such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash), systemi lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is estimate to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs ar tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient may becom comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma levels whe toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, ataxia at 3 mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mcg/mL, bu as high a concentration as 50 mcg/mL has been reported without evidence of toxicity. As muc as 25 times the therapeutic dose has been taken to result in a serum concentration over 10 mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully observed an appropriate supportive measures employed. Hemodialysis can be considered since phenytoi is not completely bound to plasma proteins. Total exchange transfusion has been used in th treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol, should b borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0362G28

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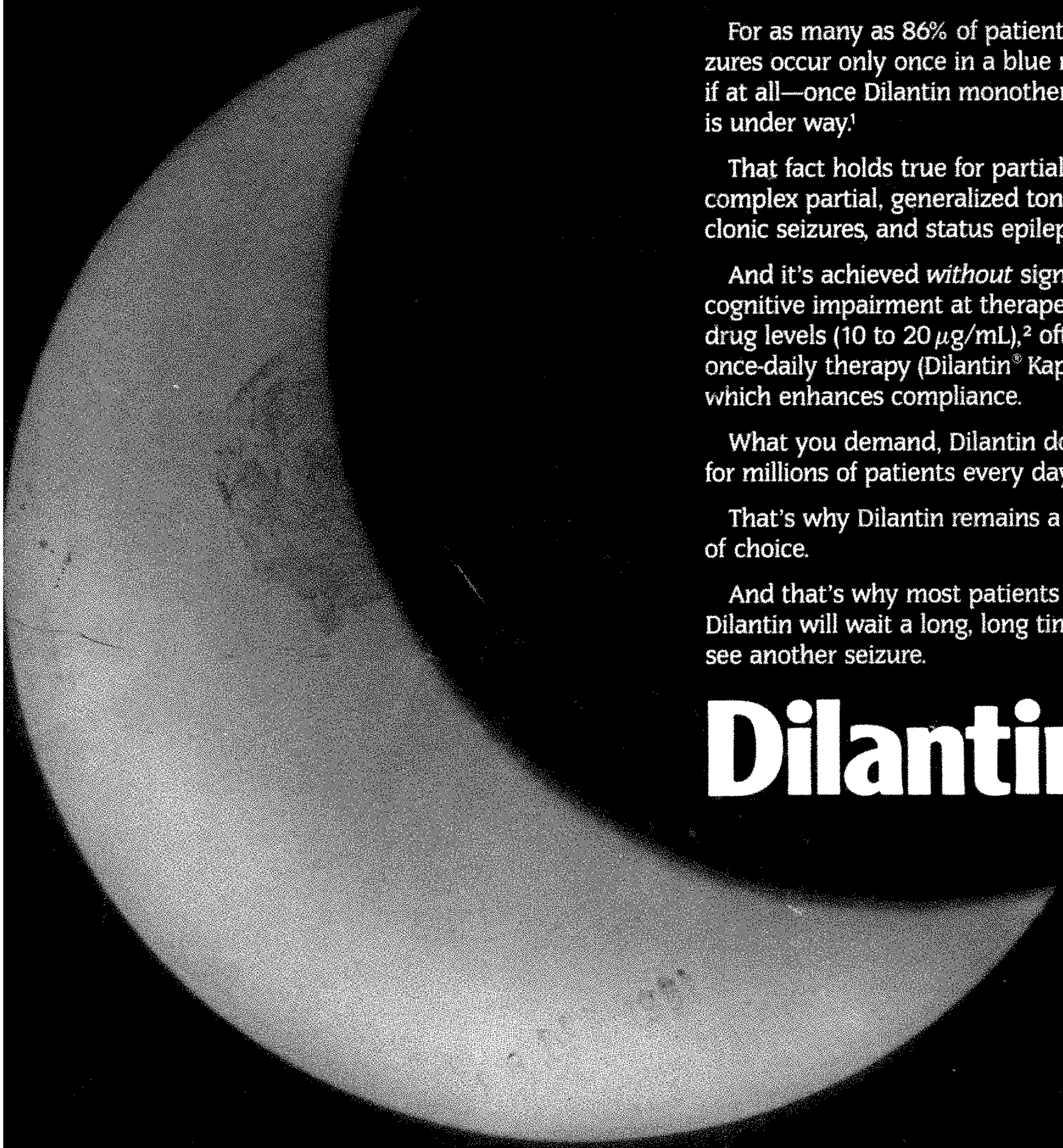
PARKE-DAVIS
Div of Warner-Lambert Co
Morris Plains, NJ 07950 USA

As rare as a seizure on Dilantin® (extended phenytoin sodium capsules, USP) 100 mg



For as many as 86% of patients, seizures occur only once in a blue moon—if at all—once Dilantin monotherapy is under way.[1]

That fact holds true for partial, complex partial, generalized tonic-clonic seizures, and status epilepticus.

And it's achieved *without* significant cognitive impairment at therapeutic drug levels (10 to 20 μg/mL),[2] often *with* once-daily therapy (Dilantin® Kapseals®), which enhances compliance.

What you demand, Dilantin does—for millions of patients every day.

That's why Dilantin remains a drug of choice.

And that's why most patients on Dilantin will wait a long, long time to see another seizure.

Dilantin®

"Once in a blue moon" describes the phenomenon in which the moon appears as a brilliant blue. Seen worldwide following the volcanic eruption of Krakatoa in 1883, the blue moon occurs only when atmospheric cloud droplets, each less than 5 μm in diameter, form in abundance—an exceedingly rare event.[3]

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References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976 31:292-296.

Please see adjacent page for brief summary of prescribing information.

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Clinical Correlates of White-Matter Changes on Magnetic Resonance Imaging Scans of the Brain
T. R. Mirsen, D. H. Lee, C. J. Wong, J. F. Diaz, A. J. Fox, V. C. Hachinski, H. Merskey

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Improved Recognition of Leukoaraiosis and Cognitive Impairment in Alzheimer's Disease
J. F. Diaz, H. Merskey, V. C. Hachinski, D. H. Lee, M. Boniferro, C. J. Wong, T. R. Mirsen, H. Fox

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Cerebrovascular Instability in a Subset of Patients With Stroke and Transient Ischemic Attack
L. Friberg, T. S. Olsen

Gangliosides in Cerebrospinal Fluid in 'Probable Alzheimer's Disease'
K. Blennow, P. Davidsson, A. Wallin, P. Fredman, C.-G. Gottfries, I. Karlsson, J.-E. Månsson, L. Svennerholm

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Paired Associate Learning in Senile Dementia of the Alzheimer Type
J. M. Duchek, M. Cheney, F. R. Ferraro, M. Storandt

Volume 48, Number 10

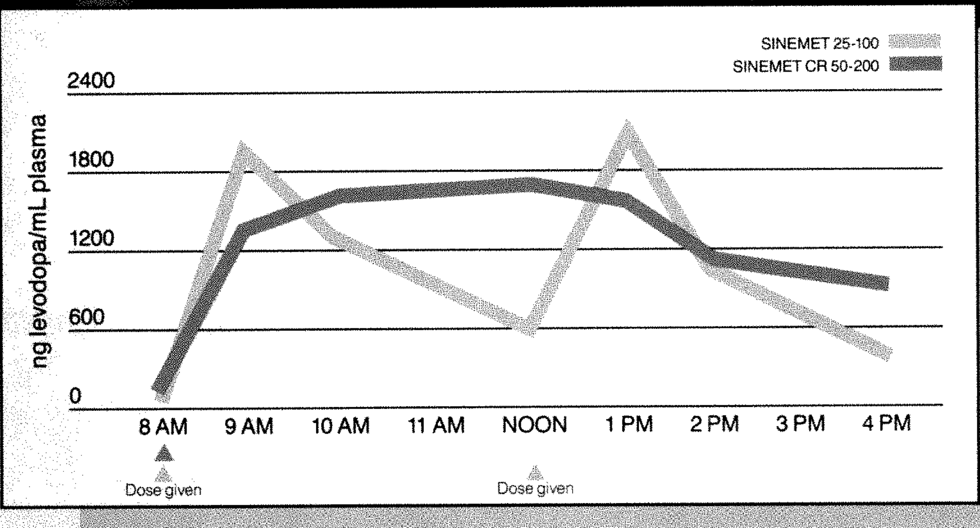
American Medical Association
Physicians dedicated to the health of America

INTRODUCING FROM DU PONT PHARMACEUTICALS
For many patients with Parkinson's disease

SINEMET® CR

(CARBIDOPA-LEVODOPA)
SUSTAINED-RELEASE

Smoother Plasma Levodopa Levels*



Less fluctuation of plasma levodopa levels with SINEMET CR vs SINEMET® (Carbidopa-Levodopa)[1]

In a clinical trial, 14 patients with mild to moderate Parkinson's disease had plasma levodopa levels measured over 8 hours after one dose of SINEMET CR, and were compared with levels over the same period after two doses of SINEMET 25-100.

Smoother plasma levodopa levels

The causes of motor fluctuations are not completely understood; *in some patients* they may be attenuated by treatment regimens that produce steady plasma levels of levodopa.

Reduced dosing frequency[2]

In a separate multicenter, double-blind trial of 202 patients with advanced Parkinson's disease, patients recorded a mean reduction of 33% in daily dosing frequency with SINEMET CR.[2]

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*Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET. The physician should be notified if such delayed responses pose a problem in treatment.

Before prescribing SINEMET CR, please see Full Prescribing Information on the following pages.

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SINEMET CR is indicated in the treatment of the symptoms of idiopath Parkinson's disease (paralysis agitans), postencephalitic parkinsonism and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication and manganese intoxication.

1. Goetz CG, Tanner CM, Shannon KM, et al: Controlled-release carbidopa/levodor (CR4-Sinemet) in Parkinson's disease patients with and without motor fluctuatior *Neurology.* 1988;38:1143-1146.
2. Hutton JT, Morris JL, Bush DF, et al: Multicenter controlled study of Sinemet CR v Sinemet (25/100) in advanced Parkinson's disease. *Neurology.* 1989;39 (suppl 2): 67-72.

- Significantly greater benefits as rated by patients previously treated with SINEMET® (Carbidopa-Levodopa)‡[2]
- Although in clinical trials, patients with moderate to severe motor fluctuations who received SINEMET® CR (Carbidopa-Levodopa) Sustained-Release *did not experience quantitatively significant reductions* in "off" time when compared to SINEMET, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.
- Significantly greater clinical improvement in patients with moderate to severe motor fluctuatio as rated by physicians**[2]
- In controlled clinical trials, patients predominantl with moderate to severe motor fluctuations while SINEMET were randomized to therapy with eithe SINEMET or SINEMET CR: *Adverse experience profile of SINEMET CR did not differ substantially from that of SINEMET.*

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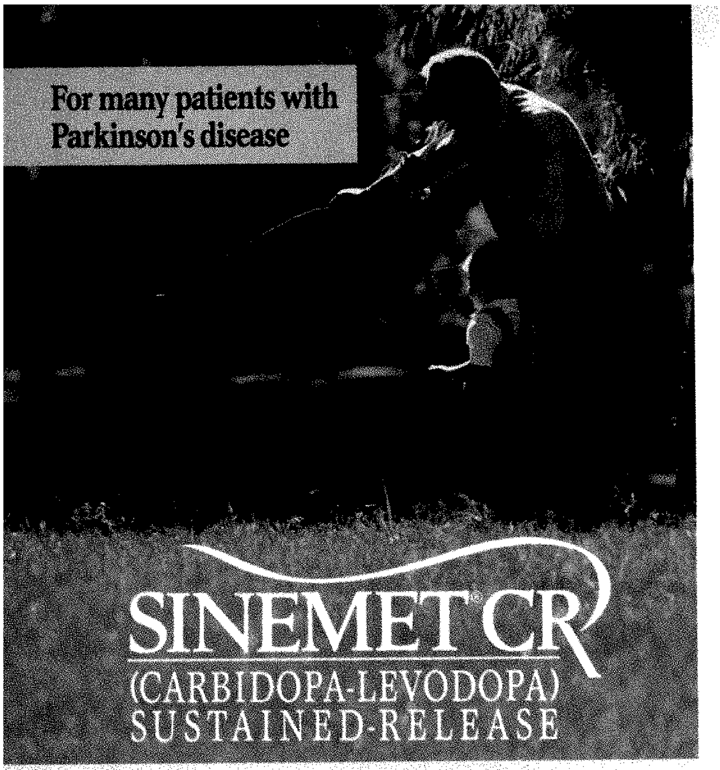
†In clinical trials of patients with moderate to severe motor fluctuations, global ratings of improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINEMET.

‡Ratings based on patients' subjective assessment of global improvement in clinical fluctuations.

**Physician ratings based on significantly greater overall improvement in patient's clinical condition after eight weeks on SINEMET CR (compared to status at beginning of double-blind phase of same trials).[2]

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight hours before SINEMET CR is started. It is necessary to individualize therapy. SINEMET CR should be substituted at a dosage that will provide approximately 25% of the previous levodopa dosage. Nonselective MAO inhibitors are contrain cated for use with SINEMET CR. These inhibitors must be discontinu at least two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the manufacturer's recommended dose of an MAO inhibitor with selectivity for MAO type B, (e.g., selegiline HCl). SINEMET CR is contraindicated i patients with known hypersensitivity to any component of this drug a in patients with narrow-angle glaucoma. Because levodopa may activ a malignant melanoma, SINEMET CR should not be used in patients with suspicious, undiagnosed skin lesions or a history of melanoma.



Guidelines for Initial Conversion from SINEMET® to SINEMET CR

(Carbidopa-Levodopa)

- Dosage with SINEMET CR should be substituted at an amount that provides approximately 10% more levodopa per day. This may be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response. (See DOSAGE AND ADMINISTRATION, *Titration.*)*
- Interval between doses of SINEMET CR should be 4-8 hours during the waking day.
- Doses and dosing intervals may be increased or decreased depending upon therapeutic response.

SINEMET Total daily dose levodopa (mg)	**SINEMET CR** Suggested dosage regimen†
300-400	1 tab b.i.d.
500-600	1½ tab b.i.d. or 1 tab t.i.d.
700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

The above is only provided as an example of conversion. Dosage must be individualized and will vary from patient to patient. This example chart reflects dosing of SINEMET CR to provide an increase of approximately 10% more levodopa.

*The bioavailability of levodopa from SINEMET CR relative to SINEMET is approximately 70%-75%.

†For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations* of enclosed Full Prescribing Information.

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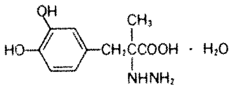
SINEMET® CR (CARBIDOPA-LEVODOPA)

SUSTAINED-RELEASE TABLETS

DESCRIPTION

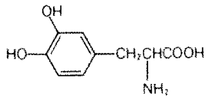
SINEMET* CR (Carbidopa-Levodopa) is a sustained-release combination of carbidopa and levodopa for t treatment of Parkinson's disease and syndrome.

Carbidopa, an inhibitor of aromatic amino acid decarboxylation, is a white, crystalline compound, slightly soluble in wa with a molecular weight of 244.3. It is designated chemically as (−)-L-α-hydrazino-α-methyl-β-(3,4-dihydroxybenzene) propar acid monohydrate. Its empirical formula is $C_{10}H_{14}N_2O_4 \bullet H_2O$ and its structural formula is:



Tablet content is expressed in terms of anhydrous carbidopa which has a molecular weight of 226.3.

Levodopa, an aromatic amino acid, is a white, crystalline compound slightly soluble in water, with a molecular wei of 197.2. It is designated chemically as (−)-L-α-amino-β-(3,4-dihydroxybenzene) propanoic acid. Its empirical formul $C_9H_{11}NO_4$ and its structural formula is



SINEMET CR is supplied as sustained-release tablets containing 50 mg of carbidopa and 200 mg of levodopa. Inac ingredients in SINEMET CR are: D & C Yellow 10, magnesium stearate, iron oxide, and other ingredients.

SINEMET CR is supplied as an oval, scored, biconvex, compressed tablet that is peach colored. The tablet is a polym based drug delivery system which controls the release of carbidopa and levodopa as it slowly erodes.

CLINICAL PHARMACOLOGY

Pharmacodynamics Current evidence indicates that symptoms of Parkinson's disease are related to depletion of d mine in the corpus striatum. Administration of dopamine is ineffective in the treatment of Parkinson's disease appare because it does not cross the blood-brain barrier. However, levodopa, the metabolic precursor of dopamine, does cross blood-brain barrier, and presumably is converted to dopamine in the brain. This is thought to be the mechanism whe levodopa relieves symptoms of Parkinson's disease.

When levodopa is administered orally it is rapidly decarboxylated to dopamine in extracerebral tissues so that only a s portion of a given dose is transported unchanged to the central nervous system. For this reason, large doses of levod are required for adequate therapeutic effect and these may often be attended by nausea and other adverse reactions, s of which are attributable to dopamine formed in extracerebral tissues.

Since levodopa competes with certain amino acids for transport across the gut wall, the absorption of levodopa ma impaired in some patients on a high protein diet.

Carbidopa inhibits decarboxylation of peripheral levodopa. It does not cross the blood-brain barrier and does not a the metabolism of levodopa within the central nervous system.

Since its decarboxylase inhibiting activity is limited to extracerebral tissues, administration of carbidopa with levo makes more levodopa available for transport to the brain.

Patients treated with levodopa therapy for Parkinson's disease may develop motor fluctuations characterized by en dose failure, peak dose dyskinesia, and akinesia. The advanced form of motor fluctuations ('on-off' phenomenon) is cha terized by unpredictable swings from mobility to immobility. Although the causes of the motor fluctuations are not c pletely understood, *in some patients* they may be attenuated by treatment regimens that produce steady plasma leve levodopa.

SINEMET CR contains 50 mg of carbidopa and 200 mg of levodopa in a sustained-release dosage form designed to rel these ingredients over a 4 to 6 hour period. With SINEMET CR there is less variation in plasma levodopa levels than SINEMET* (Carbidopa-Levodopa), the conventional formulation. *However, SINEMET CR (Carbidopa-Levodopa, Sustai Release) is less systemically bioavailable than SINEMET (Carbidopa-Levodopa) and may require increased daily doses to ac the same level of symptomatic relief as provided by SINEMET (Carbidopa-Levodopa).*

In clinical trials, patients with moderate to severe motor fluctuations *who received SINEMET CR did not experience q titatively significant reductions* in 'off' time when compared to SINEMET (Carbidopa-Levodopa). However, global ratin improvement as assessed by both patient and physician were better during therapy with SINEMET CR than with SINE (Carbidopa-Levodopa). In patients without motor fluctuations, SINEMET CR, under controlled conditions, provided the s therapeutic benefit with less frequent dosing when compared to SINEMET (Carbidopa-Levodopa).

Pyridoxine hydrochloride (vitamin B_6), in oral doses of 10 mg to 25 mg, may reverse the effects of levodopa by increa the rate of aromatic amino acid decarboxylation. Carbidopa inhibits this action of pyridoxine.

Pharmacokinetics Carbidopa reduces the amount of levodopa required to produce a given response by about 75 cent and, when administered with levodopa, increases both plasma levels and the plasma half-life of levodopa, and decre plasma and urinary dopamine and homovanillic acid.

Elimination half-life of levodopa in the presence of carbidopa is about 1.5 hours. Following SINEMET CR, the app half-life of levodopa may be prolonged because of continuous absorption.

In healthy elderly subjects (56-67 years old) the mean time to peak concentration of levodopa after a single do SINEMET CR 50-200 was about 2 hours as compared to 0.5 hours after standard SINEMET (Carbidopa-Levodopa). maximum concentration of levodopa after a single dose of SINEMET CR was about 35% of the standard SINEMET (Carbic Levodopa) (1151 vs 3256 ng/mL). The extent of availability of levodopa from SINEMET CR was about 70-75% relative to intrave levodopa or standard SINEMET (Carbidopa-Levodopa) in the elderly. The absolute bioavailability of levodopa SINEMET CR (relative to I.V.) in young subjects was shown to be only about 44%. The extent of availability and the peak centrations of levodopa were comparable in the elderly after a single dose and at steady state after t.i.d. administrati SINEMET CR 50-200. In elderly subjects, the average trough levels of levodopa at steady state after the CR tablet were a 2 fold higher than after the standard SINEMET (Carbidopa-Levodopa) (163 vs 74 ng/mL).

In these studies, using similar total daily doses of levodopa, plasma levodopa concentrations with SINEMET CR fl ated in a narrower range than with SINEMET (Carbidopa-Levodopa). Because the bioavailability of levodopa SINEMET CR relative to SINEMET (Carbidopa-Levodopa) is approximately 70-75% the daily dosage of levodopa nece to produce a given clinical response with the sustained-release formulation will usually be higher.

The extent of availability and peak concentrations of levodopa after a single dose of SINEMET CR 50-200, increas about 50% and 25%, respectively, when administered with food.

INDICATIONS AND USAGE

SINEMET CR is indicated in the treatment of the symptoms of idiopathic Parkinson's disease (paralysis agitans), po cephalitic parkinsonism, and symptomatic parkinsonism which may follow injury to the nervous system by carbon m ide intoxication and manganese intoxication.

CONTRAINDICATIONS

Nonselective MAO inhibitors are contraindicated for use with SINEMET CR. These inhibitors must be discontinued at two weeks prior to initiating therapy with SINEMET CR. SINEMET CR may be administered concomitantly with the mar turer's recommended dose of an MAO inhibitor with selectivity for MAO type B (e.g., selegiline HCl).

SINEMET CR is contraindicated in patients with known hypersensitivity to any component of this drug and in pa with narrow-angle glaucoma.

Because levodopa may activate a malignant melanoma, SINEMET CR should not be used in patients with suspic undiagnosed skin lesions or a history of melanoma.

WARNINGS

When patients are receiving levodopa without a decarboxylase inhibitor, levodopa must be discontinued at least eight before SINEMET CR is started. In order to reduce adverse reactions, it is necessary to individualize therapy. SINEM should be substituted at a dosage that will provide approximately 25 percent of the previous levodopa dosage (see DO AND ADMINISTRATION).

Carbidopa does not decrease adverse reactions due to central effects of levodopa. By permitting more levodopa to the brain, particularly when nausea and vomiting is not a dose-limiting factor, certain adverse CNS effects, e.g., dyskin will occur at lower dosages and sooner during therapy with SINEMET CR (Carbidopa-Levodopa, Sustained-Release with levodopa alone.

As with levodopa, SINEMET CR may cause involuntary movements and mental disturbances. These reactions are th to be due to increased brain dopamine following administration of levodopa. All patients should be observed caref the development of depression with concomitant suicidal tendencies. Patients with past or current psychoses sho treated with caution. The occurrence of dyskinesias may require dosage reduction.

Patients receiving SINEMET CR may develop increased dyskinesia compared to SINEMET (Carbidopa-Levodop

SINEMET CR should be administered cautiously to patients with severe cardiovascular or pulmonary disease, bro asthma, renal, hepatic or endocrine disease.

As with levodopa, care should be exercised in administering SINEMET CR to patients with a history of myocardial infarction who have residual atrial, nodal, or ventricular arrhythmias. In such patients, cardiac function should be monitored with particular care during the period of initial dosage adjustment, in a facility with provisions for intensive cardiac care.

As with levodopa, treatment with SINEMET CR may increase the possibility of upper gastrointestinal hemorrhage in patients with a history of peptic ulcer.

A symptom complex resembling the neuroleptic malignant syndrome including muscular rigidity, elevated body temperature, mental changes, and increased serum creatine phosphokinase has been reported when antiparkinsonian agents were withdrawn abruptly. Therefore, patients should be observed carefully when the dosage of SINEMET CR is reduced abruptly or discontinued, especially if the patient is receiving neuroleptics.

PRECAUTIONS

General As with levodopa, periodic evaluations of hepatic, hematopoietic, cardiovascular, and renal function are recommended during extended therapy.

Patients with chronic wide angle glaucoma may be treated cautiously with SINEMET CR provided the intraocular, pressure is well controlled and the patient is monitored carefully for changes in intraocular pressure during therapy.

Information for Patients The patient should be informed that SINEMET CR is a sustained-release formulation of carbidopa-levodopa which releases these ingredients over a 4 to 6 hour period. It is important that SINEMET CR be taken at regular intervals according to the schedule outlined by the physician. The patient should be cautioned not to change the prescribed dosage regimen and not to add any additional antiparkinson medications, including other carbidopa-levodopa preparations, without first consulting the physician.

If abnormal involuntary movements appear or get worse during treatment with SINEMET CR, the physician should be notified, as dosage adjustment may be necessary.

Patients should be advised that sometimes the onset of effect of the first morning dose of SINEMET CR may be delayed for up to 1 hour compared with the response usually obtained from the first morning dose of SINEMET (Carbidopa-Levodopa). The physician should be notified if such delayed responses pose a problem in treatment.

Patients must be advised that the whole or half tablet should be swallowed without chewing or crushing.

NOTE: The suggested advice to patients being treated with SINEMET CR is intended to aid in the safe and effective use of this medication. It is not a disclosure of all possible adverse or intended effects.

Laboratory Tests Abnormalities in laboratory tests may include elevations of liver function tests such as alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, and bilirubin. Abnormalities in blood urea nitrogen and positive Coombs test have also been reported. Commonly, levels of blood urea nitrogen, creatinine, and uric acid are lower during administration of carbidopa-levodopa preparations than with levodopa.

Carbidopa-levodopa preparations may cause a false-positive reaction for urinary ketone bodies when a test tape is used for determination of ketonuria. This reaction will not be altered by boiling the urine specimen. False-negative tests may result with the use of glucose-oxidase methods of testing for glucosuria.

Drug Interactions *Caution should be exercised when the following drugs are administered concomitantly with SINEMET CR (Carbidopa-Levodopa, Sustained-Release).*

Symptomatic postural hypotension has occurred when carbidopa-levodopa preparations were added to the treatment of patients receiving some antihypertensive drugs. Therefore, when therapy with SINEMET CR is started, dosage adjustment of the antihypertensive drug may be required. For patients receiving monoamine oxidase inhibitors, see CONTRAINDICATIONS.

There have been rare reports of adverse reactions, including hypertension and dyskinesia, resulting from the concomitant use of tricyclic antidepressants and carbidopa-levodopa preparations.

Phenothiazines and butyrophenones may reduce the therapeutic effects of levodopa. In addition, the beneficial effects of levodopa in Parkinson's disease have been reported to be reversed by phenytoin and papaverine. Patients taking these drugs with SINEMET CR should be carefully observed for loss of therapeutic response.

Carcinogenesis, Mutagenesis, Impairment of Fertility In a two-year bioassay of SINEMET (Carbidopa-Levodopa), no evidence of carcinogenicity was found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

In reproduction studies with SINEMET (Carbidopa-Levodopa), no effects on fertility were found in rats receiving doses of approximately two times the maximum daily human dose of carbidopa and four times the maximum daily human dose of levodopa (equivalent to 8 SINEMET CR tablets).

Pregnancy Pregnancy Category C. No teratogenic effects were observed in a study in mice receiving up to 20 times the maximum recommended human dose of SINEMET (Carbidopa-Levodopa). There was a decrease in the number of live pups delivered by rats receiving approximately two times the maximum recommended human dose of carbidopa and approximately five times the maximum recommended human dose of levodopa during organogenesis. SINEMET (Carbidopa-Levodopa) caused both visceral and skeletal malformations in rabbits at all doses and ratios of carbidopa/levodopa tested, which ranged from 10 times/5 times the maximum recommended human dose of carbidopa/levodopa to 20 times/10 times the maximum recommended human dose of carbidopa/levodopa.

There are no adequate or well-controlled studies in pregnant women. Use of SINEMET CR in women of childbearing potential requires that the anticipated benefits of the drug be weighed against possible hazards to mother and child.

Nursing Mothers It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when SINEMET CR is administered to a nursing mother.

Pediatric Use Safety and effectiveness in infants and children have not been established, and use of the drug in patients below the age of 18 is not recommended.

ADVERSE REACTIONS

In controlled clinical trials, patients predominantly with moderate to severe motor fluctuations, while on SINEMET (Carbidopa-Levodopa) were randomized to therapy with either SINEMET (Carbidopa-Levodopa) or SINEMET CR. The adverse experience frequency profile of SINEMET CR did not differ substantially from that of SINEMET (Carbidopa-Levodopa), as shown in Table 1.

Table 1 Clinical Adverse Experiences Occurring in 1% or Greater of Patients

Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %	Adverse Experience	**SINEMET CR** n=491 %	**SINEMET** (Carbidopa-Levodopa) n=524 %
Dyskinesia	16.5	12.2	Back Pain	1.6	0.6
Nausea	5.5	5.7	Dry Mouth	1.4	1.1
Hallucinations	3.9	3.2	Anorexia	1.2	1.1
Confusion	3.7	2.3	Diarrhea	1.2	0.6
Dizziness	2.9	2.3	Insomnia	1.2	1.0
Depression	2.2	1.3	Orthostatic Hypotension	1.0	1.1
Urinary Tract Infection	2.2	2.3	Shoulder Pain	1.0	0.6
Headache	2.0	1.9	Chest Pain	1.0	0.8
Dream Abnormalities	1.8	0.8	Muscle Cramps	0.8	1.0
Dystonia	1.8	0.8	Paresthesia	0.8	1.1
Vomiting	1.8	1.9	Urinary Frequency	0.8	1.1
Upper Respiratory Infection	1.8	1.0	Dyspepsia	0.6	1.1
Dyspnea	1.6	0.4	Constipation	0.2	1.5
'On-Off' Phenomena	1.6	1.1			

Abnormal laboratory findings occurring at a frequency of 1% or greater in approximately 443 patients who received SINEMET CR and 475 who received SINEMET (Carbidopa-Levodopa) during controlled clinical trials included: decreased hemoglobin and hematocrit; elevated serum glucose; white blood cells, bacteria and blood in the urine.

The adverse experiences observed in patients in uncontrolled studies were similar to those seen in controlled clinical studies.

Other adverse experiences reported overall in clinical trials in 748 patients treated with SINEMET CR, listed by body system in order of decreasing frequency, include:

Nervous System/Psychiatric: Chorea, somnolence, falling, anxiety disorder, disorientation, decreased mental acuity, gait abnormalities, extrapyramidal disorder, agitation, nervousness, sleep disorders, memory impairment.

Body as a Whole: Asthenia, fatigue, abdominal pain, orthostatic effects.

Digestive: Gastrointestinal pain, dysphagia, heartburn.

Cardiovascular: Palpitation, essential hypertension, hypotension, myocardial infarction.

Special Senses: Blurred vision.

Metabolic: Weight loss.

Skin: Rash.

Respiratory: Cough, pharyngeal pain, common cold.

Urogenital: Urinary incontinence.

Musculoskeletal: Leg pain.

Laboratory Tests: Decreased white blood cell count and serum potassium; increased BUN, serum creatinine and serum LDH; protein and glucose in the urine.

Other adverse experiences have been reported with various cabidopa-levodopa formulations and may occur with SINEMET CR:

Nervous System/Psychiatric: Mental changes including paranoid ideation, psychotic episodes, depression with suicidal tendencies and dementia; convulsions (however, a causal relationship has not been established); bradykinetic episodes.

Gastrointestinal: Gastrointestinal bleeding, development of duodenal ulcer. 76194

Cardiovascular: Cardiac irregularities, phlebitis. 625

Hematologic: Hemolytic and nonhemolytic anemia, thrombocytopenia, leukopenia, agranulocytosis.

Laboratory Tests: Abnormalities in alkaline phosphatase, SGOT (AST), SGPT (ALT), lactic dehydrogenase, bilirubin, protei bound iodine, Coombs test.

Other adverse reactions that have been reported with levodopa are:

Nervous System: Numbness, increased hand tremor, muscle twitching, blepharospasm (which may be taken as an ear sign of excess dosage, consideration of dosage reduction may be made at this time), trismus, activation of latent Horner syndrome.

Psychiatric: Delusions, euphoria.

Gastrointestinal: Bitter taste, sialorrhea, bruxism, hiccups, flatulence, burning sensation of tongue.

Metabolic: Weight gain, edema.

Integumentary: Malignant melanoma (see also CONTRAINDICATIONS), flushing, increased sweating, dark sweat, loss of ha

Genitourinary: Urinary retention, urinary incontinence, dark urine, priapism.

Miscellaneous: Faintness, hoarseness, malaise, hot flashes, sense of stimulation, bizarre breathing patterns, neurolept malignant syndrome.

OVERDOSAGE

Management of acute overdosage with SINEMET CR is the same as with levodopa. Pyridoxine is not effective in reversi the actions of SINEMET CR.

General supportive measures should be employed, along with immediate gastric lavage. Intravenous fluids should administered judiciously and an adequate airway maintained. Electrocardiographic monitoring should be instituted a the patient carefully observed for the development of arrhythmias; if required, appropriate antiarrhythmic therapy shou be given. The possibility that the patient may have taken other drugs as well as SINEMET CR should be taken into consider tion. To date, no experience has been reported with dialysis; hence, its value in overdosage is not known.

Based on studies in which high doses of levodopa and/or carbidopa were administered, a significant proportion of ra and mice given single oral doses of levodopa of approximately 1500-2000 mg/kg are expected to die. A significant propo tion of infant rats of both sexes are expected to die at a dose of 800 mg/kg. A significant proportion of rats are expected die after treatment with similar doses of carbidopa. The addition of carbidopa in a 1:10 ratio with levodopa increases t dose at which a significant proportion of mice are expected to die to 3360 mg/kg.

DOSAGE AND ADMINISTRATION

SINEMET CR tablets contain carbidopa (50 mg) and levodopa (200 mg) in a 1:4 ratio. The daily dosage of SINEMET CR mu be determined by careful titration. Patients should be monitored closely during the dose adjustment period, particular with regard to appearance or worsening of involuntary movements, dyskinesias or nausea. SINEMET CR may be administere as whole or as half-tablets which should not be chewed or crushed.

Standard drugs for Parkinson's disease, other than levodopa without a decarboxylase inhibitor, may be used concom tantly while SINEMET CR is being administered, although their dosage may have to be adjusted.

Since carbidopa prevents the reversal of levodopa effects caused by pyridoxine, SINEMET CR can be given to patien receiving supplemental pyridoxine (vitamin B_6).

Initial Dosage *Patients currently treated with conventional carbidopa-levodopa preparations:* Dosage with SINEMET C should be substituted at an amount that provides approximately 10% more levodopa per day, although this may need be increased to a dosage that provides up to 30% more levodopa per day depending on clinical response (see DOSAG AND ADMINISTRATION, TITRATION). The interval between doses of SINEMET CR should be 4-8 hours during the waki day. (See CLINICAL PHARMACOLOGY, *Pharmacodynamics*).

A guideline for *initiation* of SINEMET CR is shown in Table II.

TABLE II Guidelines for Initial Conversion from SINEMET (Carbidopa-Levodopa) to SINEMET CR	**SINEMET (Carbidopa-Levodopa)** Total Daily Dose* Levodopa (mg)	**SINEMET CR** Suggested Dosage Regimen
	300-400	1 tab b.i.d.
	500-600	1½ tab b.i.d. or 1 tab t.i.d.
	700-800	A total of 4 tabs in 3 or more divided doses (e.g., 1½ tab a.m., 1½ tab early p.m., and 1 tab later p.m.)
	900-1000	A total of 5 tabs in 3 or more divided doses (e.g., 2 tabs a.m., 2 tabs early p.m., and 1 tab later p.m.)

*For dosing ranges not shown in the table see DOSAGE AND ADMINISTRATION, *Initial Dosage—Patients currently treated with conventional carbidopa-levodopa preparations.*

Patients currently treated with levodopa without a decarboxylase inhibitor: Levodopa must be discontinued at least eight hou before therapy with SINEMET CR is started. SINEMET CR should be substituted at a dosage that will provide approximate 25% of the previous levodopa dosage. In patients with mild to moderate disease, the initial dose is usually 1 tablet SINEMET CR b.i.d.

Patients not receiving levodopa: In patients with mild to moderate disease, the initial recommended dose is 1 tablet SINEMET CR b.i.d. Initial dosage should not be given at intervals of less than 6 hours.

Titration Following initiation of therapy, doses and dosing intervals may be increased or decreased depending upon the apeutic response. Most patients have been adequately treated with 2 to 8 tablets per day, administered as divided dos at intervals ranging from 4 to 8 hours during the waking day. Higher doses (12 or more tablets per day) and shorter interva (less than 4 hours) have been used, but are not usually recommended.

When doses of SINEMET CR are given at intervals of less than 4 hours, and/or if the divided doses are not equal, it recommended that the smaller doses be given at the end of the day.

An interval of at least 3 days between dosage adjustments is recommended.

Maintenance Because Parkinson's disease is progressive, periodic clinical evaluations are recommended; adjustme of the dosage regimen of SINEMET CR may be required.

Addition of Other Antiparkinson Medications Anticholinergic agents, dopamine agonists, and amantadine can given with SINEMET CR. Dosage adjustment of SINEMET CR may be necessary when these agents are added.

A dose of SINEMET (Carbidopa-Levodopa) 25-100 or 10-100 (one half or a whole tablet) can be added to the dosage re men of SINEMET CR in selected patients with advanced disease who need additional levodopa for a brief time during da time hours.

Interruption of Therapy Patients should be observed carefully if abrupt reduction or discontinuation of SINEMET CR required, especially if the patient is receiving neuroleptics. (See WARNINGS).

If general anesthesia is required, SINEMET CR may be continued as long as the patient is permitted to take oral medic tion. If therapy is interrupted temporarily, the usual dosage should be administered as soon as the patient is able to ta oral medication.

HOW SUPPLIED

SINEMET CR 50-200 (Carbidopa-Levodopa) SUSTAINED-RELEASE TABLETS containing 50 mg of carbidopa and 200 m of levodopa, are peach-colored, oval, scored, biconvex, compressed tablets, coded 521. They are supplied as follows:

NDC 0056-0521-68 bottles of 100

NDC 0056-0521-28 unit dose packages of 100.

Storage Avoid temperatures above 30°C (86°F). Store in a tightly closed container.

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ARCHIVES

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ORIGINAL CONTRIBUTIONS

Clinical Correlates of White-Matter Changes on Magnetic Resonance Imaging Scans of the Brain 1015
Thomas R. Mirsen, MD; Donald H. Lee, DM; Cindy J. Wong, MSc;
J. Fernando Diaz, MD; Allan J. Fox, MD;
Vladimir C. Hachinski, MD, DSc(Med);
Harold Merskey, DM, London, Ontario

Improved Recognition of Leukoaraiosis and Cognitive Impairment in Alzheimer's Disease 1022
J. Fernando Diaz, MD; Harold Merskey, DM;
Vladimir C. Hachinski, MD; Donald H. Lee, MD; Mary Boniferro, MEd;
Cindy J. Wong, MSc, London, Ontario;
Thomas R. Mirsen, MD, Camden, NJ;
Hannah Fox, MBBS, London, Ontario

Cerebrovascular Instability in a Subset of Patients With Stroke and Transient Ischemic Attack 1026
Lars Friberg, MD, Tom Skyhøj Olsen, MD, Copenhagen, Denmark

Gangliosides in Cerebrospinal Fluid in 'Probable Alzheimer's Disease' 1032
Kaj Blennow, MD, PhD; Pia Davidsson, PhD; Anders Wallin, MD, PhD;
Pam Fredman, PhD; Carl-Gerhard Gottfries, MD, PhD;
Ingvar Karlsson, MD, PhD; Jan-Eric Månsson, PhD;
Lars Svennerholm, MD, PhD, Hisings Backa, Sweden

Paired Associate Learning in Senile Dementia of the Alzheimer Type 1038
Janet M. Duchek, PhD; Marshall Cheney, MA; F. Richard Ferraro, PhD;
Martha Storandt, PhD, St Louis, Mo

Monozygotic Twins With Seizures: Shared Characteristics 1041
Rosalind A. Segal, MD, PhD; Catherine Chapman, MD;
John Barlow, MD, Boston, Mass

Tremor at Onset: Predictor of Cognitive and Motor Outcome in Parkinson's Disease? 1049
Linda A. Hershey, MD, PhD; Brian J. Feldman, MD; Kye Y. Kim, MD;
Chris Commichau; David G. Lichter, MD, Buffalo, NY

Continued on page 999.

EDITORIAL BOARD

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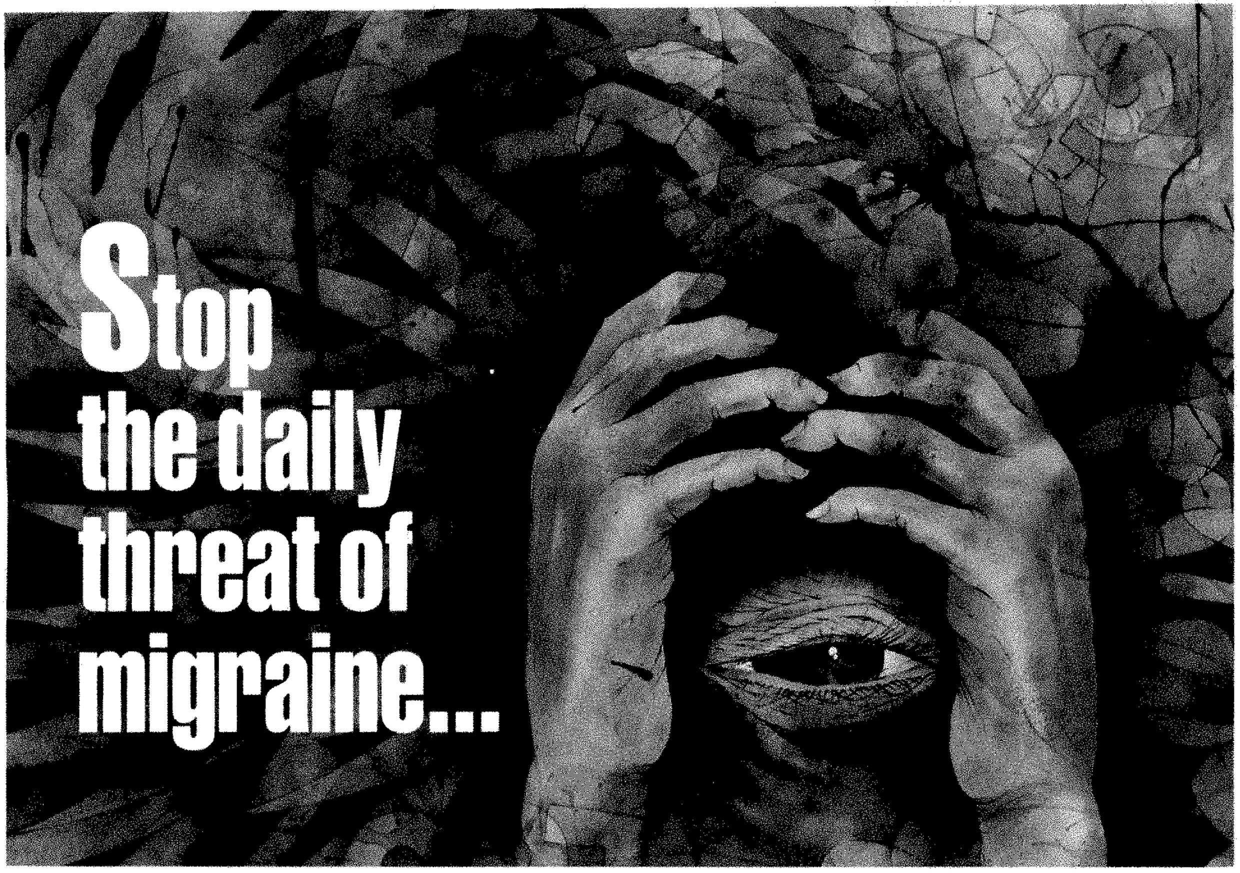

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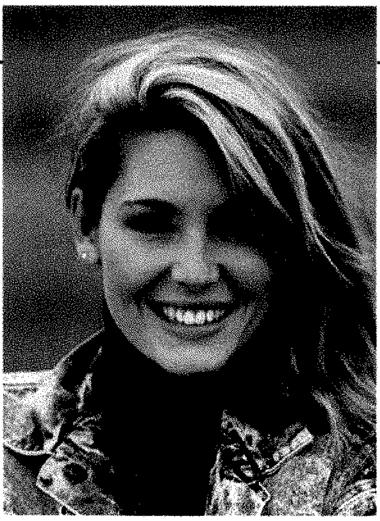

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INDERAL® LA (propranolol HCl) Long Acting Capsules
BRIEF SUMMARY OF PRESCRIBING INFORMATION:
CONSULT THE PACKAGE LITERATURE FOR FULL PRESCRIBING INFORMATION.

CONTRAINDICATIONS. INDERAL is contraindicated in 1) cardiogenic shock; 2) sinus bradycardia and greater than first-degree block; 3) bronchial asthma; 4) congestive heart failure (see WARNINGS), unless the failure is secondary to a tachyarrhythmia treatable with INDERAL.

WARNINGS. CARDIAC FAILURE: Sympathetic stimulation may be a vital component supporting circulatory function in patients with congestive heart failure, and its inhibition by beta-blockade may precipitate more severe failure. Although beta blockers should be avoided in overt congestive heart failure, if necessary, they can be used with close follow-up in patients with a history of failure who are well compensated and are receiving digitalis and diuretics. Beta-adrenergic blocking agents do not abolish the inotropic action of digitalis on heart muscle.

IN PATIENTS WITHOUT A HISTORY OF HEART FAILURE, continued use of beta blockers can, in some cases, lead to cardiac failure. Therefore, at the first sign or symptom of heart failure, the patient should be digitalized and/or treated with diuretics, and the response observed closely, or INDERAL should be discontinued (gradually, if possible).

IN PATIENTS WITH ANGINA PECTORIS, there have been reports of exacerbation of angina and, in some cases, myocardial infarction, following *abrupt* discontinuance of INDERAL therapy. Therefore, when discontinuance of INDERAL is planned, the dosage should be gradually reduced over at least a few weeks, and the patient should be cautioned against interruption or cessation of therapy without the physician's advice. If INDERAL therapy is interrupted and exacerbation of angina occurs, it usually is advisable to reinstitute INDERAL therapy and take other measures appropriate for the management of unstable angina pectoris. Since coronary artery disease may be unrecognized, it may be prudent to follow the above advice in patients considered at risk of having occult atherosclerotic heart disease who are given propranolol for other indications.

Nonallergic Bronchospasm (eg, chronic bronchitis, emphysema) – PATIENTS WITH BRONCHOSPASTIC DISEASES SHOULD IN GENERAL NOT RECEIVE BETA BLOCKERS. INDERAL should be administered with caution since it may block bronchodilation produced by endogenous and exogenous catecholamine stimulation of beta receptors.

MAJOR SURGERY: The necessity or desirability of withdrawal of beta-blocking therapy prior to major surgery is controversial. It should be noted that the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.

INDERAL, like other beta blockers, is a competitive inhibitor of beta-receptor agonists and its effects can be reversed by administration of such agents, eg, dobutamine or isoproterenol. However, such patients may be subject to protracted severe hypotension. Difficulty in starting and maintaining the heartbeat has also been reported with beta blockers.

DIABETES AND HYPOGLYCEMIA: Use beta blockers with caution in diabetic patients if a beta-blocking agent is required. Beta blockers may mask tachycardia occurring with hypoglycemia; other manifestations such as dizziness and sweating may not be significantly affected. Following insulin-induced hypoglycemia, propranolol may cause a delay in the recovery of blood glucose to normal levels.

THYROTOXICOSIS: Beta blockade may mask certain clinical signs of hyperthyroidism, thus abrupt withdrawal of propranolol may be followed by an exacerbation of symptoms of hyperthyroidism, including thyroid storm. Propranolol may change thyroid-function tests, increasing T_4 and reverse T_3, and decreasing T_3.

IN PATIENTS WITH WOLFF-PARKINSON-WHITE SYNDROME, several cases have been reported in which, after propranolol, tachycardia was replaced by severe bradycardia requiring a demand pacemaker. In one case this resulted after an initial dose of 5 mg propranolol.

PRECAUTIONS. GENERAL: Use with caution in patients with impaired hepatic or renal function. INDERAL is not indicated for the treatment of hypertensive emergencies.

Beta-adrenoreceptor blockade can cause reduction of intraocular pressure. Patients should be told that INDERAL may interfere with the glaucoma screening test. Withdrawal may lead to a return of increased intraocular pressure.

CLINICAL LABORATORY TESTS: Elevated blood urea levels in patients with severe heart disease, elevated serum transaminase, alkaline phosphatase, lactate dehydrogenase.

DRUG INTERACTIONS: Patients receiving catecholamine-depleting drugs such as reserpine should be closely observed if INDERAL is administered. The added catecholamine-blocking action may produce an excessive reduction of resting sympathetic nervous activity resulting in hypotension, marked bradycardia, vertigo, syncopal attacks, or orthostatic hypotension.

Caution should be exercised when patients receiving a beta blocker are administered a calcium-channel-blocking drug, especially intravenous verapamil, as both agents may depress myocardial contractility or atrioventricular conduction. On rare occasions, the concomitant intravenous use of a beta blocker and verapamil has resulted in serious adverse reactions, especially in patients with severe cardiomyopathy, congestive heart failure or recent myocardial infarction.

Aluminum hydroxide gel greatly reduces intestinal absorption of propranolol.

Ethanol slows the rate of absorption of propranolol.

Phenytoin, phenobarbitone, and *rifampin* accelerate propranolol clearance.

Chlorpromazine, when used concomitantly with propranolol, results in increased plasma levels of both drugs.

Antipyrine and *lidocaine* have reduced clearance when used concomitantly with propranolol.

Thyroxine may result in a lower than expected T_3 concentration when used concomitantly with propranolol.

Cimetidine decreases the hepatic metabolism of propranolol, delaying elimination and increasing blood levels.

Theophylline clearance is reduced when used concomitantly with propranolol.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: There was no evidence of significant drug-induced toxicity in rats or mice, employing doses up to 150 mg/kg/day over an 18-month period. There were no drug-related tumorigenic effects at any dosage levels. No impairment of fertility attributable to the drug was seen in animal reproductive studies.

PREGNANCY: Pregnancy Category C. INDERAL has been shown to be embryotoxic in animal studies at doses about 10 times greater than the maximum recommended human dose. There are no adequate and well-controlled studies in pregnant women. Use during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS: INDERAL is excreted in human milk. Exercise caution when INDERAL is administered to a nursing woman.

PEDIATRIC USE: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS. Most adverse effects have been mild and transient and have rarely required the withdrawal of therapy.

Cardiovascular: Bradycardia; congestive heart failure; intensification of AV block; hypotension; paresthesia of hands; thrombocytopenic purpura; arterial insufficiency, usually of the Raynaud type.

Central Nervous System: Light-headedness; mental depression manifested by insomnia, lassitude, weakness, fatigue; reversible mental depression progressing to catatonia; visual disturbances; hallucinations; vivid dreams; an acute reversible syndrome characterized by disorientation for time and place, short-term memory loss, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics. For immediate formulations, fatigue, lethargy, and vivid dreams appear dose related.

Gastrointestinal: Nausea, vomiting, epigastric distress, abdominal cramping, diarrhea, constipation, mesenteric arterial thrombosis, ischemic colitis.

Allergic: Pharyngitis and agranulocytosis, erythematous rash, fever combined with aching and sore throat, laryngospasm, and respiratory distress.

Respiratory: Bronchospasm.

Hematologic: Agranulocytosis, nonthrombocytopenic purpura, thrombocytopenic purpura.

Auto-Immune: In extremely rare instances, systemic lupus erythematosus has been reported.

Miscellaneous: Alopecia, LE-like reactions, psoriasiform rashes, dry eyes, male impotence, and Peyronie's disease have been reported rarely. The oculomucocutaneous reactions associated with practolol have not been reported with propranolol.

DOSAGE AND ADMINISTRATION: INDERAL LA provides propranolol hydrochloride in a sustained-release capsule for administration once daily. If patients are switched from INDERAL Tablets to INDERAL LA Capsules, care should be taken to assure that the desired therapeutic effect is maintained. INDERAL LA should not be considered a simple mg-for-mg substitute for INDERAL. INDERAL LA has different kinetics and produces lower blood levels. Retitration may be necessary, especially to maintain effectiveness at the end of the 24-hour dosing interval.

For management of hypertension, angina pectoris, migraine, and hypertrophic subaortic stenosis the dosage must be individualized. Usual initial dose is 80 mg once daily.

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PEDIATRIC DOSAGE – At this time the data on the use of the drug in this age group are too limited to permit adequate directions for use.

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ARCHIVES

Tritiated Imipramine Binding: A Peripheral Marker for Serotonin in Parkinson's Disease 1052
Mary Sano, PhD; Michael Stanley, PhD; Arlene Lawton, RN; Lucien Coté, MD; Janet Williams, DSW; Yaakov Stern, PhD; Karen Marder, MD; Richard Mayeux, MD, New York, NY

Ultrasound Findings in Spontaneous Carotid Artery Dissection: The Value of Duplex Sonography 1057
Matthias Sturzenegger, MD, Bern, Switzerland

High-Intensity Area in the Deep White Matter Indicating Hemodynamic Compromise in Internal Carotid Artery Occlusive Disorders 1067
Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; Shinya Yamaguchi, MD; Toshihiko Miyoshi, MD; Jun Kimura, MD; Junji Konishi, MD, Kyoto, Japan

Automatic Memory Processes in Patients With Multiple Sclerosis 1072
Jordan Grafman, PhD, Bethesda, Md; Stephen Rao, PhD; Linda Bernardin, MS; Gary J. Leo, DO, Milwaukee, Wis

Importance of Intrathecal Synthesis of IgD in Multiple Sclerosis: A Combined Clinical, Immunologic, and Magnetic Resonance Imaging Study 1076
Mohammad K. Sharief, MB, ChB, MPhil, London, United Kingdom; Romain Hentges, MD, Brussels, Belgium

Serologic Evidence of *Campylobacter jejuni/coli* Enteritis in Patients With Guillain-Barré Syndrome 1080
Ruben Gruenewald, PhD, New York, NY; Allan H. Ropper, MD, Boston, Mass; Hermy Lior, MSc, Ottawa, Ontario; Joseph Chan; Richard Lee; Vernaleah S. Molinaro, New York, NY

Autonomic Nervous Function in Progressive Supranuclear Palsy 1083
J. Gert van Dijk, MD; Joost Haan, MD, PhD; Monique Koenderink; Raymund A. C. Roos, MD, PhD, Leiden, the Netherlands

OBSERVATIONS

Acute Hemorrhagic Leukoencephalitis: A Successful Recovery 1086
David Seales, MD, PhD, Melvin Greer, MD, Gainesville, Fla

Isolated Congenital Hemianopia Caused by Prenatal Injury to the Optic Radiation 1088
Nicola K. Ragge, MRCP FCOphth; A. James Barkovich, MD; William F. Hoyt, MD, San Francisco, Calif; Scott R. Lambert, MD, Atlanta, Ga

Visual Hallucinations and Racing Thoughts on Eye Closure After Minor Surgery 1091
C. Miller Fisher, MD, Boston, Mass

Continued on page 1001.

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INDEX TO ADVERTISERS

American Electroencephalographic Society 1008
Anesthesiology Alumni Association of Florida, Inc. 1000

Basel Pharmaceuticals 1000A-B, 1056A-B
Berlex Imaging 1040A-D
Bio-Logic Systems Corp. 1036-1037

Computational Diagnostics 1000

F. A. Davis Company 1005, 1055
Du Pont Pharmaceuticals .... Cover 2-995

Eli Lilly & Company 1008A-D

Miles Pharmaceuticals 1046-1048

Parke-Davis .... 1014, Cover 3-Cover 4

Sandoz Pharmaceuticals 1065-1066

TECA Corporation 1002

Wyeth-Ayerst Laboratories 997-998

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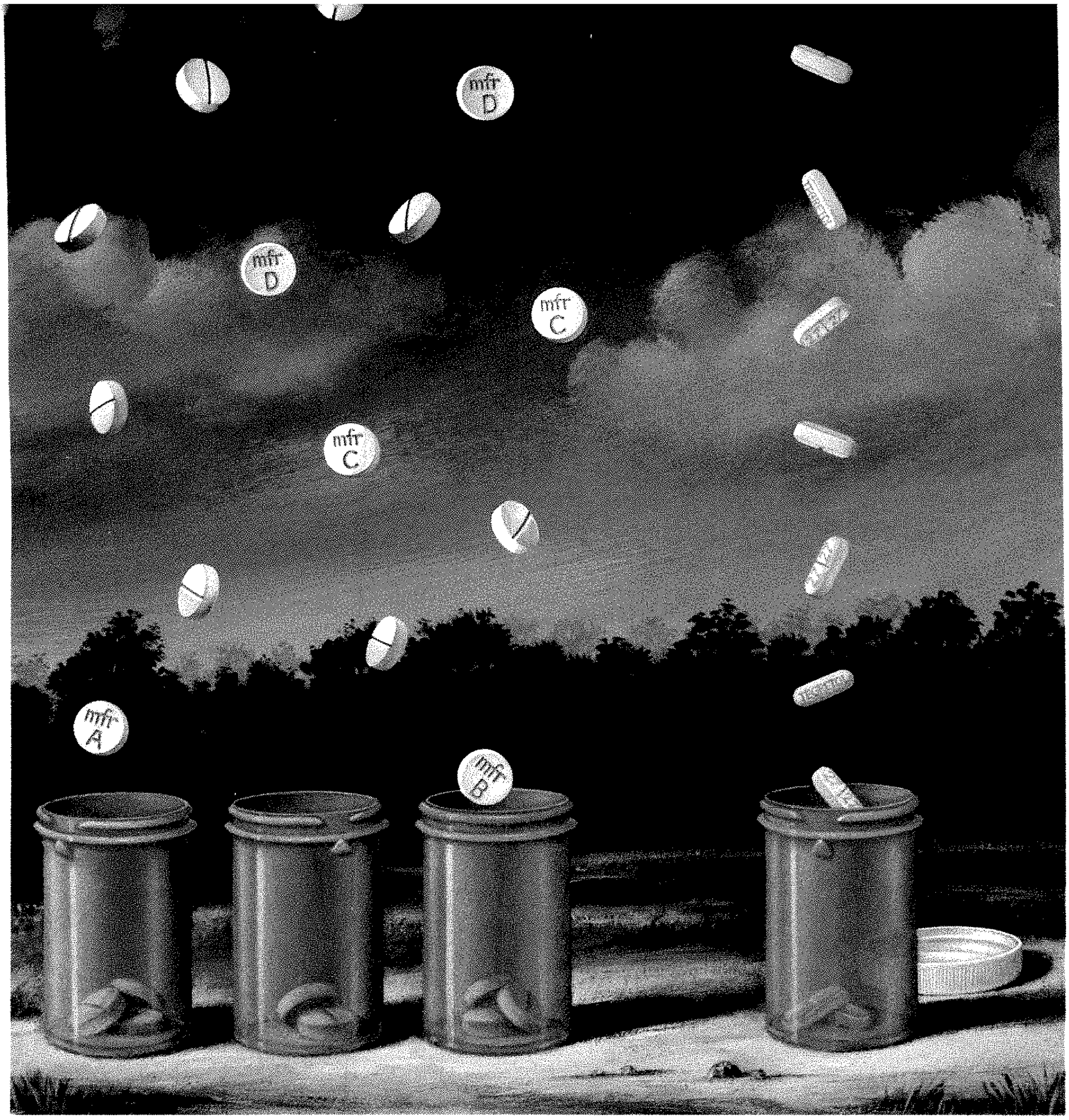

From refill to refill... which carbamazepine will your patient get next?

TEGRETOL is indicated for children 6 years and older and adults.

Because of the potential for serious hematologic adverse reactions, it is important that you become thoroughly familiar with the full Prescribing Information for TEGRETOL on the following page, especially the boxed warning.

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Sign each prescription on the line that prevents substitution, or add the phrase required in your state to prevent substitution:

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WARNING

APLASTIC ANEMIA AND AGRANULOCYTOSIS HAVE BEEN REPORTED IN ASSOCIATION WITH THE USE OF TEGRETOL. DATA FROM A POPULATION-BASED CASE CONTROL STUDY DEMONSTRATE THAT THE RISK OF DEVELOPING THESE REACTIONS IS 5-8 TIMES GREATER THAN IN THE GENERAL POPULATION. HOWEVER, THE OVERALL RISK OF THESE REACTIONS IN THE UNTREATED GENERAL POPULATION IS LOW, APPROXIMATELY SIX PATIENTS PER ONE MILLION POPULATION PER YEAR FOR AGRANULOCYTOSIS AND TWO PATIENTS PER ONE MILLION POPULATION PER YEAR FOR APLASTIC ANEMIA.

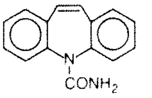
ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.

BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

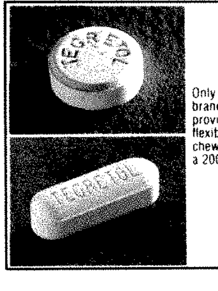
Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.



Only TEGRETOL,
brand of carbamazepine,
provides the prescribing
flexibility of a 100-mg scored
chewable tablet, as well as
a 200-mg scored tablet

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System: Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin. Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System: Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System: Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System: Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System: Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System: Aching joints and muscles, and leg cramps.

Metabolism: Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other: Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD 50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration: Irregular breathing, respiratory depression.

Cardiovascular System: Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles: Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract: Nausea, vomiting.

Kidneys and Bladder: Anuria or oliguria, urinary retention.

Laboratory Findings: Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug: Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption: Activated charcoal, laxatives.

Measures to Accelerate Elimination: Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression. Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions: Diazepam or barbiturates.

Warning: Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance: Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities: If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE).

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE).

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

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Robert A. Hauser, MD, C. Warren Olanow, MD, Tampa, Fla

In Reply
T. S. Elizan, MD; D. A. Moros, MD; M. D. Yahr, MD, New York, NY

Trends in Parkinson's Disease Mortality in Italy 1010
Adriano Chió, MD; Corrado Magnani, MD; Giampiero Tolardo, MD;
Davide Schiffer, MD, Turin, Italy

A Commentary on Steroid Treatment in Multiple Sclerosis 1011
Chris H. Polman, MD; Hans E. van der Wiel, MD;
Jacobus C. Netelenbos, MD, PhD; G. Jaap J. Teule, MD, PhD;
Johan C. Koetsier, MD, PhD, Amsterdam, the Netherlands

Epidural Steroids Are Safe and Effective When Given Appropriately 1012
William E. Strong, MD, Roger Wesley, MD, Fort Sam Houston, Tex;
Alon P. Winnie, MD, Chicago, Ill

In Reply
Dewey A. Nelson, MD, Newark, Del

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Index to Advertisers 1000

Instructions for Authors 1003

Calendar 1004

Classified Advertising 1093

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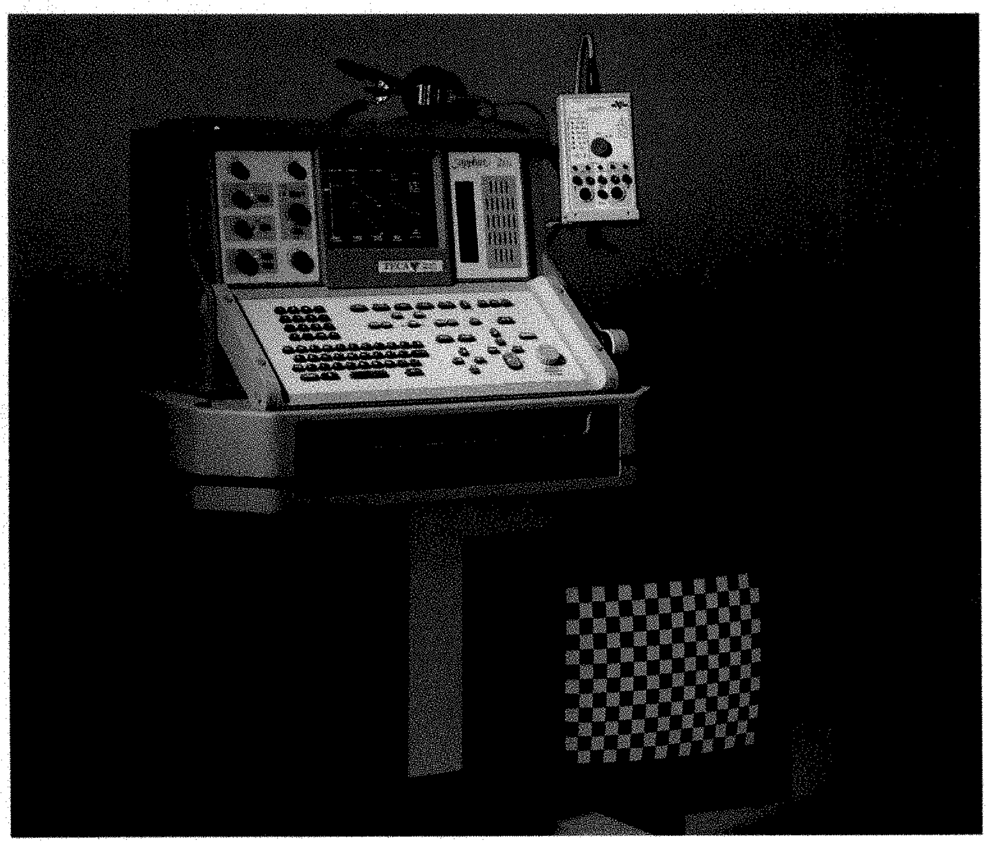

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Nov	6-10	"Progress in Understanding Postconcussion Syndrome," Four Seasons Hotel, Dallas, Tex. Contact Ann McCormick, Southern California Neuropsychiatric Institute, 6794 La Jolla Blvd, La Jolla, CA 92037; (619) 454-2102.
	8	"Contemporary Concepts of Headache Management for the Neurologist," Farmington, Conn. Contact Susan Crawford, Neurology Department, University of Connecticut School of Medicine, 263 Farmington Ave, Farmington, CT 06030; (203) 679-3186.
	16	"Selegiline: New Applications in Neurological and Psychiatric Disorders," New York, NY. Contact New York University Medical Center, Postgraduate Medical School, 550 First Ave, New York, NY 10016; (212) 263-5295.
	22-24	Second International Headache Research Seminar, Copenhagen, Denmark. Contact Mrs Vibe Halling, Secretary, Second International Headache Research Seminar, Department of Neurology, Gentofte Hospital, Niels Andersens Vej 65, DK-2900 Hellerup, Copenhagen, Denmark.
	27-31	International Symposium on Cerebrovascular Disorders, Goiana-Goiás, Brazil.
Dec	6	"Current Neuro-Ophthalmology," Ritz-Carlton Buckhead, Atlanta, Ga. Contact Emory University School of Medicine, Office of Continuing Medical Education, 1440 Clifton Rd, Atlanta, GA 30322; (404) 727-5695.
	6-7	"Molecular and Cellular Approaches to the Treatment of Brain Disease," Penta Hotel, New York, NY. Contact Ivan Bodis-Wollner, MD, Box 1052, Association for Research in Nervous and Mental Disease, Mount Sinai Hospital, One Gustave L. Levy Pl, New York, NY 10029; (212) 348-8133.

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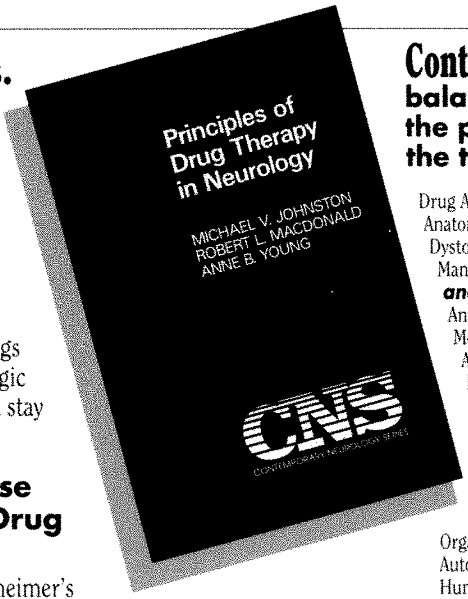
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Books

Clinical Neurophysiology Update, edited by J. E. Desmedt, vol 1, **Neuromonitoring in Surgery,** 377 pp, with illus; vol 2, **Computer-Aided Electromyography and Expert Systems,** 320 pp, with illus, Amsterdam, the Netherlands, Elsevier, 1989.

This series, edited by Professor Desmedt, who has been very active in the field of clinical neurophysiology for many years, follows the first series, *Clinical Neurophysiology,* published in 1973, and the second series, *Clinical Neurophysiology Progress,* published in 1981.

Volume 1 contains 20 chapters written by world authorities dealing with neuromonitoring techniques in surgery. This field has been developing rapidly because of new technology and is very important in surgical interventions on brain, spinal cord and roots, and peripheral nerves. The techniques help the operating team to assess function during a procedure to avoid neurologic damage. These new neuromonitoring techniques require the training of a new group of neuroanesthesiologists-clinical neurophysiologists, who can document preservation of neural function during difficult surgical procedures. This area of clinical neurophysiology should continue to develop and already has shown its value in surgical therapy. Included in this volume are chapters dealing with somatosensory evoked potentials, auditory nerve and brain-stem responses, transcranial stimulation, neuromuscular transmission, peripheral nerve recordings, spinal cord potentials, and seizure monitoring. The techniques are well-described and illustrated. Experience and results of using the techniques in various diseases and procedures are presented. A large reference list is provided at the end of the volume. This volume is highly recommended to all physicians, physiologists, and technicians who are interested in neurologic function and how it may be altered during surgical procedures. All clinical neurophysiology laboratories should be using these techniques, and this volume will be helpful in their use and interpretation.

Volume 2 stresses computers and new technology in the study and analysis of electromyelographic (EMG) signals and its value in neuromuscular disease. Each of the 23 chapters is written by world authorities in the area. The volume is divided into sections on needle EMG motor-unit recordings, surface EMG, EMG-interference patterns, applications of EMG analysis and artificial intelligence, and expert systems in neuromuscular diagnosis. The chapters are well written and have adequate illustrations. The reference list is comprehensive and located at the end of the volume.

Quantitative EMG has been available for many years and depends on technology as well as the ease of its use and the dependability of its results. Most laboratories using these techniques are now research oriented, since the techniques, to date, have not been reliable by themselves for accurate neuromuscular diagnoses or therapy. However, they remain important in the physiologic study and interpretation of neuromuscular function. This volume is recommended for students, engineers, and clinical neurophysiologists who are active in this area of research. Clinical neurologists will not find it helpful in their practice at this time.

RICHARD F. MAYER, MD
Baltimore, Md

Textbook of Performing Arts Medicine, edited by Robert Thayer Sataloff, Alice G. Brandfonbrener, and Richard J. Lederman, 432 pp, with illus, $88, New York, NY, Raven Press, 1991.

The publication of *Textbook of Performing Arts Medicine* marks another milestone in the growth of this new multidisciplinary specialty, complementing the recent arrivals of annual conferences, peer-reviewed journals, and professional societies. The editors of this concise volume are among the leaders in the field, Lederman being one of the leading neurologists in performing arts medicine. Since the field is still relatively early in its evolution, often there is a dearth of scientific data on which to base clinical practice. The authors and editors have done an admirable job of combining the available literature with their own considerable experience to produce a very useful text.

The 15 chapters are all well referenced and well illustrated. The major clinical entities in performing arts medicine—musculoskeletal pain syndromes and neurologic impairment of the upper extremities in instrumentalists, voice problems in singers, and lower extremity injuries in dancers—are covered well in several of the longer chapters. The chapter on voice care includes a suggested clinical database for the singer with problems. A similar outline for the hurting instrumentalist would have been helpful; the recommended workup is spread out over three chapters. The discussion of neurologic problems is comprehensive and covers both performance-induced and other performance-impairing conditions.

Three chapters are devoted to the psychological problems of performers, but this book does not offer a consolidated review of performance anxiety. Several other relevant topics are reviewed in other chapters: eye problems and hearing loss, reproductive difficulties among female dancers, and temporomandibular joint problems. The book opens nicely with a historical review of the development of the field and an epidemiologic overview of performers' problems. The closing chapter, on legal aspects of the health care of performers, is devoted almost entirely to malpractice issues. A discussion of workers' compensation issues would have been relevant here. An index is provided.

This book should become the standard reference for clinicians in a variety of specialties who see performing artists, especially musicians. Use of the book does not presuppose a sophisticated knowledge of music or dance. Whether it will be used by performers and their teachers remains to be seen. One hopes that it will enhance the interaction between performers and those who care for them.

RALPH A. MANCHESTER, MD
Rochester, NY

Neck and Arm Pain, ed 3, by R. Cailliet, 226 pp, $16.95, Philadelphia, Pa, FA Davis Co Publishers, 1991.

This work addresses the evaluation and treatment of commonly encountered symptoms in the general practice of medicine. The early chapters are concerned with anatomy, cervical nerves, and posture. The analysis of symptoms based on pain mechanisms is well prepared and focused on the diverse structures within the cervical spine and spinal cord that may be the source of pain. The section dedicated to whiplash syndrome is well done, and the author's approach to different types of treatment is nicely presented. All of the chapters contain numerous, well-drawn illustrations by Dr Cailliet. Unfortunately, at times they are presented on pages that do not correspond to the actual text. The chapters concerned with spondylitic myelopathy and thoracic outlet syndrome pay little attention to possible surgical intervention.

The bibliography at the end of each chapter is substantial and current.

This short, focused work contains much useful information that should be most helpful to a wide group of health professionals.

RICHARD SATRAN, MD
Rochester, NY

Advances in Neurology, volume 55, **Neurobehavioral Problems in Epilepsy**, edited by Dennis B. Smith, David M. Treiman, and Michael R. Trimble, 485 pp, $135, New York, NY, Raven Press, 1990.

The *Advances in Neurology* series has been delivering useful, state-of-the-art reviews of clinical topics for almost 20 years. This, the 55th volume in the series, is quite in keeping with the high standards that have been established. The volume belongs in the library of all behavioral neurologists, epileptologists, and clinicians who have a substantial commitment to treatment of, and research in, epilepsy.

Does epilepsy predispose to violence? To psychosis? What is our current understanding of the interictal personality disorders of epilepsy? Is carbamazepine *really* "easier" on cognition than its competitors? Which anticonvulsants are psychotropics, and how valuable are they in actual practice? These controversies and others receive measured consideration within the chapters of this book. For example, with regard to the question of interictal behavioral disturbances that develop among patients with temporal lobe epilepsy, the contrasting viewpoints of Janice Stevens, Michael Trimble, and Frank Benson are all presented. Jerome Engel provides a complementary review of more basic physiologic and animal research of relevance to the issue. The book does not attempt to provide a synthesis of these divergent perspectives but lets these senior scholars speak for themselves.

There is a solid, international character to the list of contributors, and most speak with the authority of academic centers, where there is ongoing neuropsychiatric research into behavioral aspects of epilepsy. The UCLA group is well represented among the authorship as well as the National Institute of Mental Health, Bethesda, Md, and the National and Maudsley Hospitals, London, England. German, Swiss, and French groups are also represented. References for most chapters are encyclopedic. The quality of presentation by the publisher is high, and few typographical errors have slipped by the editors.

At this juncture in the review, I would normally add some comments about weaknesses and failings in the book. For *Neurobehavioral Problems in Epilepsy* I have none. This book is well done, topical, and valuable to researchers and clinicians alike. It should serve a wide audience and come to be widely cited.

RANDOLPH B. SCHIFFER, MD
Rochester, NY

Peripheral Neuropathy in Childhood, by R. Ouvrier, J. G. McLeod, and J. Pollard, 252 pp, $84, New York, NY, Raven Press, 1990.

Neuropathies in children are uncommon and often nettlesome clinical problems. Because these slowly evolving disorders can produce pes cavus or scoliosis before their neuropathic nature is appreciated, these children are likely to be seen by pediatricians and orthopedists long before they are referred to neurologists. Most neurologists have limited experience with childhood neuropathies and will welcome the advent of this readable, slender, and focused resource. The authors have long-standing and broadly based interests in the childhood neuropathies. Dr Ouvrier, the pediatric neurologist at Children's Hospital Camperdown, Sydney, Australia, has worked for years with his colleagues at the University of Sydney. Drs McLeod and Pollard are leading figures in the clinical, physiological, and pathological assessment of neuropathies. The resulting volume covers in an authoritative fashion the major heritable neuropathies and the inflammatory demyelinating neuropathies. It more briefly presents the rare metabolic and idiopathic conditions. Adequate attention is directed toward the organization, pathophysiology, and clinical assessment of peripheral nerves so that the descriptions of abnormalities in individual diseases can be followed by the nonspecialist and the nonneurologist. Thus, while this book will be read through by pediatric neurologists and by neuromuscular specialists, it undoubtedly will be useful to pediatricians, orthopedists, and house staff in their evaluation of individual patients.

After the introductory chapters, the book is organized by diseases. Written in a straightforward style, the text has a formality that recalls earlier times. For example, at the end of several discussions, "Case Histories," some credited to colleagues, are effectively presented in a fashion reminiscent of Weir Mitchell. This leisurely and attractive feature contrasts with the brevity with which some disorders of particular current interest are presented. For example, mitochondrial cytopathies are dismissed in one sentence, and no mention of the explosion of clinically useful molecular approaches in the heritable amyloidoses is offered.

This is a cautious book. The literature is extensively cited and controversies are dutifully noted. At times, the reader may wish that the authors were not quite so dutiful and evenhanded. The preface suggests that "this book is written from a strong personal perspective based, where possible, on our own clinical experience. It is likely that some will disagree with our experience, but when possible we prefer to state an opinion and have it refuted rather than to equivocate." This warning may refer to the authors' firm stance that Dejerine-Sottas disease is a distinct recessive disorder with characteristic features and to the attention given to "Hereditary Motor and Sensory Neuropathy of Neuronal Type With Onset in Early Childhood" (the latter is a disorder in need of an acro-, epo-, or other short "nym"). These are disorders about which Dr Ouvrier has contributed original work, and the discussions make clear the authors' views. However, in other areas, despite their extensive experience, they are content to cite opinions and data from the literature. For example, their experience with 60 cases of childhood Guillain-Barré syndrome is not further detailed or called on to support opinions. Their experience would have been welcome.

Finally, this book has the advantage of its Australian origins and reflects the sharing of information and the concentration of experience that characterize the Australian health system. The authors explicitly acknowledge cases and data from other Australian workers, particularly Dr Lloyd Shield in Melbourne, and implicitly acknowledge the Australian system that (in common with the British, Canadian, and New Zealand systems) allows the collection of specific diseases and problems in centers. The authors undoubtedly see most of the pediatric peripheral nerve disease in New South Wales. Whatever defects these health care systems might have, they encourage the referral and central collection of material from rare disorders. Few individuals in this country have had such experience with peripheral nerve disease in children, and, with the continued dissemination of subspecialty expertise, even fewer will in the future. This book will remain a useful clinical resource.

JOHN W. GRIFFIN, MD
Baltimore, Md

ANNUAL MEETING AND COURSES

American Electroencephalographic Society
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The **Annual Meeting** of the Society will be held December 10-12 at the Wyndham Franklin Plaza Hotel in Philadelphia, Pennsylvania. The program will include Symposia on: **The Changing Contribution of Electrophysiology to Epileptology**, **EEG-Neurophysiology-Epileptogenesis**, and **Advances in Evoked Potentials**, as well as Scientific Sessions, posters, and a technical exhibit.

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For more information, contact:

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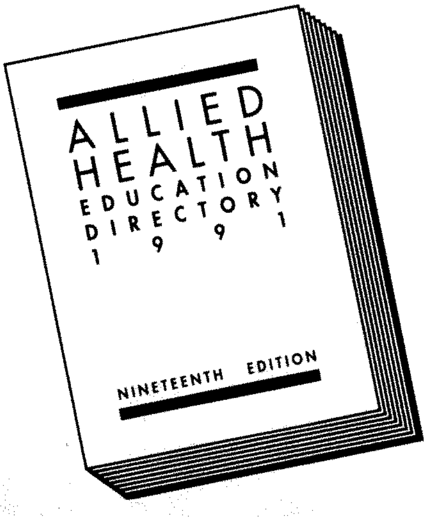

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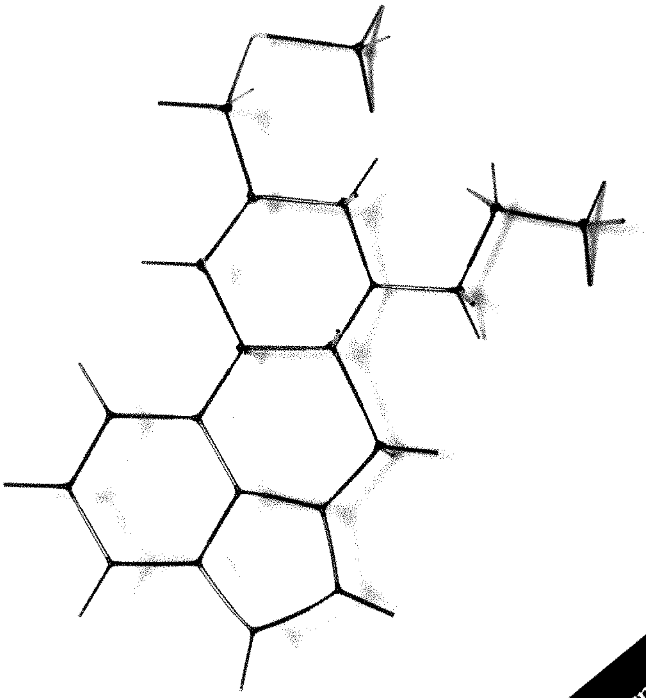

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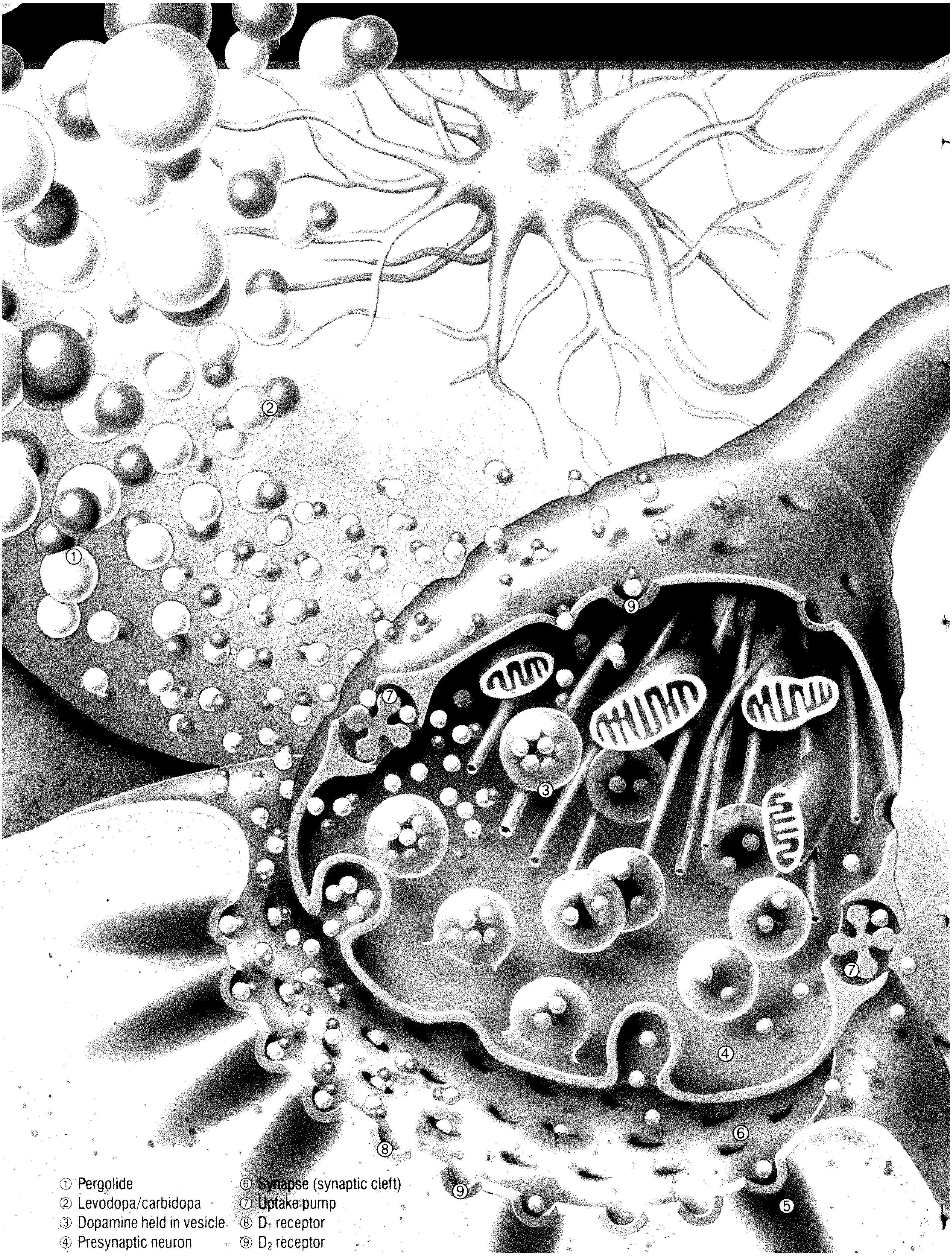
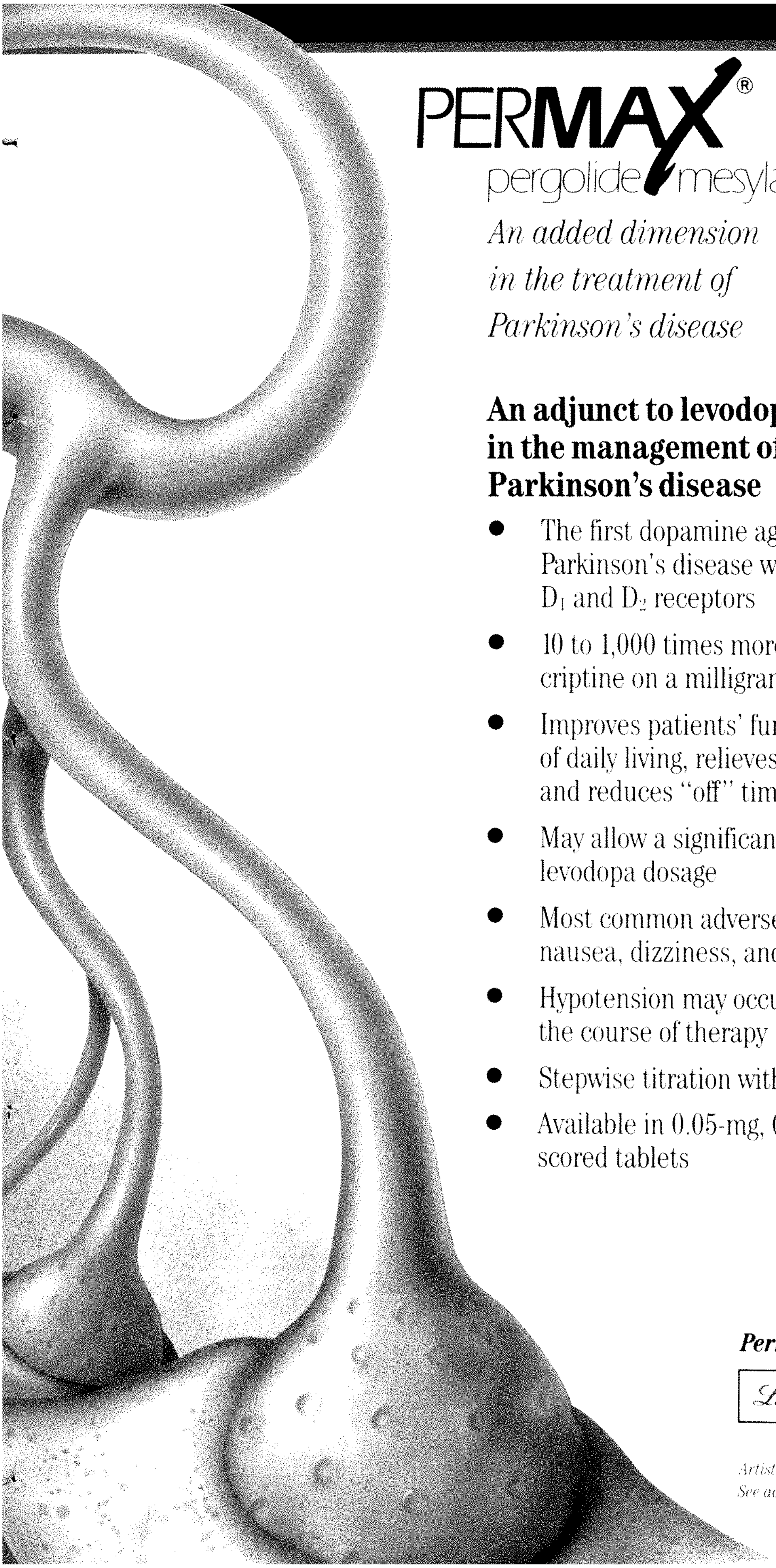


① Pergolide
② Levodopa/carbidopa
③ Dopamine held in vesicle
④ Presynaptic neuron
⑤
⑥ **Synapse** (synaptic cleft)
⑦ **Uptake pump**
⑧ D_1 receptor
⑨ D_2 receptor



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Brief Summary. Consult the package insert for complete prescribing information.

Indications and Usage: Permax is indicated as adjunctive treatment to levodopa/carbidopa in the management of the signs and symptoms of Parkinson's disease.

Evidence to support the efficacy of pergolide mesylate as an antiparkinsonian adjunct was obtained in a multicenter study enrolling 376 patients with mild to moderate Parkinson's disease who were intolerant to levodopa/carbidopa as manifested by moderate to severe dyskinesia and/or on-off phenomena. On average, the sample of patients evaluated had been on levodopa/carbidopa for 3.9 years (range, two days to 16.8 years). The administration of pergolide mesylate permitted a 5% to 30% reduction in the daily dose of levodopa. On average, these patients treated with pergolide mesylate maintained an equivalent or better clinical status than they exhibited at baseline.

Contraindications: Pergolide mesylate is contraindicated in patients who are hypersensitive to this drug or other ergot derivatives.

Warnings: *Symptomatic Hypotension* —In clinical trials, approximately 10% of patients taking pergolide mesylate with levodopa vs 7% taking placebo with levodopa experienced symptomatic orthostatic and/or sustained hypotension, especially during initial treatment. With gradual dosage titration, tolerance to the hypotension usually develops. It is, therefore, important to warn patients of the risk, to begin therapy with low doses, and to increase the dosage in carefully adjusted increments over a period of three to four weeks.

Hallucinosis —In controlled trials, pergolide mesylate with levodopa caused hallucinosis in about 14% of patients as opposed to 3% taking placebo with levodopa. This was of sufficient severity to cause discontinuation of treatment in about 3% of those enrolled; tolerance to this untoward effect was not observed.

Fatalities —In the placebo-controlled trial, two of 187 patients treated with placebo died as compared with one of 189 patients treated with pergolide mesylate. Of the 2,299 patients treated with pergolide mesylate in premarketing studies evaluated as of October 1988, 143 died while on the drug or shortly after discontinuing the drug. The patient population under evaluation was elderly, ill, and at high risk for death. It seems unlikely that pergolide mesylate played any role in these deaths, but the possibility that pergolide shortens survival of patients cannot be excluded with absolute certainty.

In particular, a case-by-case review of the clinical course of the patients who died failed to disclose any unique set of signs, symptoms, or laboratory results that would suggest that treatment with pergolide caused their deaths. Sixty-eight percent (68%) of the patients who died were 65 years of age or over. No death (other than a suicide) occurred within the first month of treatment; most of the patients who died had been on pergolide for years. A relative frequency of the causes of death by organ system are: pulmonary failure/pneumonia, 35%; cardiovascular, 30%; cancer, 11%; unknown, 8.4%; infection, 3.5%; extrapyramidal syndrome, 3.5%; stroke, 2.1%; dysphagia, 2.1%; injury, 1.4%; suicide, 1.4%; dehydration, 0.7%; glomerulonephritis, 0.7%.

Precautions: *General* —Caution should be exercised when administering pergolide mesylate to patients prone to cardiac dysrhythmias.

In a study comparing pergolide mesylate and placebo, patients taking pergolide mesylate were found to have significantly more episodes of atrial premature contractions (APCs) and sinus tachycardia.

The use of pergolide mesylate in patients on levodopa may cause and/or exacerbate preexisting states of confusion and hallucinations (*see* Warnings). Also, the abrupt discontinuation of pergolide mesylate in patients receiving it chronically as an adjunct to levodopa may precipitate the onset of hallucinations and confusion; these may occur within a span of several days. Discontinuation of pergolide should be undertaken gradually whenever possible, even if the patient is to remain on levodopa.

The administration of pergolide mesylate to patients receiving levodopa may cause and/or exacerbate preexisting dyskinesia.

Information for Patients —Patients and their families should be informed of the common adverse consequences of the use of pergolide mesylate (*see* Adverse Reactions) and the risk of hypotension (*see* Warnings).

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Patients should be advised to notify their physician if they are breast feeding an infant.

Laboratory Tests —No specific laboratory tests are deemed essential for the management of patients on Permax. Periodic routine evaluation of all patients, however, is appropriate.

Drug Interactions —Dopamine antagonists, such as the neuroleptics (phenothiazines, butyrophenones, thioxanthines) or metoclopramide, ordinarily should not be administered concurrently with Permax (a dopamine agonist); these agents may diminish the effectiveness of Permax.

Because pergolide mesylate is approximately 90% associated with plasma proteins, caution should be exercised if pergolide mesylate is coadministered with other drugs known to affect protein binding.

Carcinogenesis, Mutagenesis, and Impairment of Fertility —A two-year carcinogenicity study was conducted in mice using dietary levels of pergolide mesylate equivalent to oral doses of 0.6, 3.7, and 36.4 mg/kg/day in males and 0.6, 4.4, and 40.8 mg/kg/day in females. A two-year study in rats was conducted using dietary levels equivalent to oral doses of 0.04, 0.18, and 0.88 mg/kg/day in males and 0.05, 0.28, and 1.42 mg/kg/day in females. The highest doses tested in the mice and rats were approximately 340 and 12 times the maximum human oral dose administered in controlled clinical trials (6 mg/day equivalent to 0.12 mg/kg/day).

A low incidence of uterine neoplasms occurred in both rats and mice. Endometrial adenomas and carcinomas were observed in rats. Endometrial sarcomas were observed in mice. The occurrence of these neoplasms is probably attributable to the high estrogen/progesterone ratio which would occur in rodents as a result of the prolactin-inhibiting action of pergolide mesylate. The endocrine mechanisms believed to be involved in the rodents are not present in humans. However, even though there is no known correlation between uterine malignancies occurring in pergolide-treated rodents and human risk, there are no human data to substantiate this conclusion.

Pergolide mesylate was evaluated for mutagenic potential in a battery of tests that included an Ames bacterial mutation assay, a DNA repair assay in cultured rat hepatocytes, a point-mutation assay in cultured L5178Y cells, and a determination of chromosome alteration in bone marrow cells of Chinese hamsters. A weak mutagenic response was noted in the in vitro mammalian cell-point-mutation assay using L5178Y cells only after metabolic activation with rat liver microsomes. No mutagenic effects were obtained in the two other in vitro assays and in the in vivo assay. The relevance of these findings to humans is unknown.

A fertility study in male and female mice showed that fertility was maintained at 0.6 and 1.7 mg/kg/day but decreased at 5.6 mg/kg/day. Prolactin has been reported to be involved in stimulating and maintaining progesterone levels required for implantation in mice and, therefore, the impaired fertility at high dose may occur because of depressed prolactin levels.

Usage in Pregnancy - Pregnancy Category B —Reproduction studies were conducted in mice at doses of 5, 16, and 45 mg/kg/day and in rabbits at doses of 2, 6, and 16 mg/kg/day. The highest doses tested in mice and rabbits were 375 and 133 times the 6 mg/day maximum human dose administered in controlled clinical trials. In these studies, there was no evidence of harm to the fetus due to pergolide mesylate.

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There are, however, no adequate and well-controlled studies in pregnant women. Among women who received pergolide mesylate for endocrine disorders in premarketing studies, there were 33 pregnancies that resulted in healthy babies and four pregnancies that resulted in congenital abnormalities (two major, two minor); a causal relationship has not been established. Because human data are limited and because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers —It is not known whether this drug is excreted in human milk. The pharmacologic action of pergolide mesylate suggests that it may interfere with lactation. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions to pergolide mesylate in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use —Safety and effectiveness in children have not been established.

Adverse Reactions: *Commonly Observed* —In premarketing clinical trials, the most commonly observed adverse events associated with use of pergolide mesylate which were not seen at an equivalent incidence among placebo-treated patients were: nervous system complaints, including dyskinesia, hallucinations, somnolence, insomnia; digestive complaints, including nausea, constipation, diarrhea, dyspepsia; and respiratory system complaints, including rhinitis.

Associated With Discontinuation of Treatment —Twenty-seven percent (27%) of approximately 1,200 patients receiving pergolide mesylate for treatment of Parkinson's disease in premarketing clinical trials in the US and Canada discontinued treatment due to adverse events. The events most commonly causing discontinuation were related to the nervous system (15.5%), primarily hallucinations (7.8%) and confusion (1.8%).

Fatalities - *See* Warnings.

Incidence in Controlled Clinical Trials —The table that follows enumerates adverse events that occurred at a frequency of 1% or more among patients taking pergolide mesylate who participated in the premarketing controlled clinical trials comparing pergolide mesylate with placebo. In a double-blind, controlled study of six months' duration, patients with Parkinson's disease were continued on levodopa/carbidopa and were randomly assigned to receive either pergolide mesylate or placebo as additional therapy.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side-effect incidence rate in the population studied.

Incidence of Treatment-Emergent Adverse Experiences in the Placebo-Controlled Clinical Trial

Body System/ Adverse Event*	Percentage of Patients Reporting Events Pergolide Mesylate N = 189	Placebo N = 187
Body as a Whole		
Pain	7.0	2.1
Abdominal pain	5.8	2.1
Injury, accident	5.8	7.0
Headache	5.3	6.4
Asthenia	4.2	4.8
Chest pain	3.7	2.1
Flu syndrome	3.2	2.1
Neck pain	2.7	1.6
Back pain	1.6	2.1
Surgical procedure	1.6	<1
Chills	1.1	0
Face edema	1.1	0
Infection	1.1	0
Cardiovascular		
Postural hypotension	9.0	7.0
Vasodilatation	3.2	<1
Palpitation	2.1	<1
Hypotension	2.1	<1
Syncope	2.1	1.1
Hypertension	1.6	1.1
Arrhythmia	1.1	<1
Myocardial infarction	1.1	<1
Digestive		
Nausea	24.3	12.8
Constipation	10.6	5.9
Diarrhea	6.4	2.7
Dyspepsia	6.4	2.1
Anorexia	4.8	2.7
Dry mouth	3.7	<1
Vomiting	2.7	1.6
Hemic and Lymphatic		
Anemia	1.1	<1
Metabolic and Nutritional		
Peripheral edema	7.4	4.3
Edema	1.6	0
Weight gain	1.6	0
Musculoskeletal		
Arthralgia	1.6	2.1
Bursitis	1.6	<1
Myalgia	1.1	<1
Twitching	1.1	0
Nervous System		
Dyskinesia	62.4	24.6
Dizziness	19.1	13.9
Hallucinations	13.8	3.2
Dystonia	11.6	8.0
Confusion	11.1	9.6
Somnolence	10.1	3.7
Insomnia	7.9	3.2
Anxiety	6.4	4.3
Tremor	4.2	7.5
Depression	3.2	5.4
Abnormal dreams	2.7	4.3
Personality disorder	2.1	<1
Psychosis	2.1	0
Abnormal gait	1.6	1.6
Akathisia	1.6	0
Extrapyramidal syndrome	1.6	1.1
Incoordination	1.6	<1
Paresthesia	1.6	3.2
Akinesia	1.1	1.1
Hypertonia	1.1	0
Neuralgia	1.1	<1
Speech disorder	1.1	1.6
Respiratory System		
Rhinitis	12.2	5.4
Dyspnea	4.8	1.1
Epistaxis	1.6	<1
Hiccup	1.1	0
Skin and Appendages		
Rash	3.2	2.1
Sweating	2.1	2.7
Special Senses		
Abnormal vision	5.8	5.4
Diplopia	2.1	0
Taste perversion	1.6	0
Eye disorder	1.1	0
Urogenital System		
Urinary frequency	2.7	6.4
Urinary tract infection	2.7	3.7
Hematuria	1.1	<1

*Events reported by at least 1% of patients receiving pergolide mesylate are included.

Events Observed During the Premarketing Evaluation of Permax —This section reports event frequencies evaluated as of October 1988 for adverse events ocurring in a group of approximately 1,800 patients who took multiple doses of pergolide mesylate. The conditions and duration of exposure to pergolide mesylate varied greatly, involving well-controlled studies as well as experience in open and uncontrolled clinical settings. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with pergolide mesylate cannot be determined.

The following enumeration by organ system describes events in terms of their relative frequency of reporting in the data base. Events of major clinical importance are also described in the Warnings and Precautions sections.

The following definitions of frequency are used: frequent adverse events are defined as those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Body as a Whole —*Frequent:* headache, asthenia, accidental injury, abdominal pain, chest pain, back pain, flu syndrome, neck pain, fever; *Infrequent:* facial edema, chills, enlarged abdomen, malaise, neoplasm, hernia, pelvic pain, sepsis, cellulitis, moniliasis, abscess, jaw pain, hypothermia; *Rare:* acute abdominal syndrome, LE syndrome.

Cardiovascular System —*Frequent:* postural hypotension, syncope, hypertension, palpitations, vasodilatations, congestive heart failure; *Infrequent:* myocardial infarction, tachycardia, heart arrest, abnormal electrocardiogram, angina pectoris, thrombophlebitis, bradycardia, ventricular extrasystoles, cerebrovascular accident, ventricular tachycardia, cerebral ischemia, atrial fibrillation, varicose vein, pulmonary embolus, AV block, shock; *Rare:* vasculitis, pulmonary hypertension, pericarditis, migraine, heart block, cerebral hemorrhage.

Digestive System —*Frequent:* nausea, vomiting, dyspepsia, diarrhea, constipation, dry mouth, dysphagia; *Infrequent:* flatulence, abnormal liver function tests, increased appetite, salivary gland enlargement, thirst, gastroenteritis, gastritis, periodontal abscess, intestinal obstruction, nausea and vomiting, gingivitis, esophagitis, cholelithiasis, tooth caries, hepatitis, stomach ulcer, melena, hepatomegaly, hematemesis, eructation; *Rare:* sialadenitis, peptic ulcer, pancreatitis, jaundice, glossitis, fecal incontinence, duodenitis, colitis, cholecystitis, aphthous stomatitis, esophageal ulcer.

Endocrine System —*Infrequent:* hypothyroidism, adenoma, diabetes mellitus, ADH inappropriate; *Rare:* endocrine disorder, thyroid adenoma.

Hemic and Lymphatic System —*Frequent:* anemia; *Infrequent:* leukopenia, lymphadenopathy, leukocytosis, thrombocytopenia, petechia, megaloblastic anemia, cyanosis; *Rare:* purpura, lymphocytosis, eosinophilia, thrombocythemia, acute lymphoblastic leukemia, polycythemia, splenomegaly.

Metabolic and Nutritional System —*Frequent:* peripheral edema, weight loss, weight gain; *Infrequent:* dehydration, hypokalemia, hypoglycemia, iron deficiency anemia, hyperglycemia, gout, hypercholesteremia; *Rare:* electrolyte imbalance, cachexia, acidosis, hyperuricemia.

Musculoskeletal System —*Frequent:* twitching, myalgia, arthralgia; *Infrequent:* bone pain, tenosynovitis, myositis, bone sarcoma, arthritis; *Rare:* osteoporosis, muscle atrophy, osteomyelitis.

Nervous System —*Frequent:* dyskinesia, dizziness, hallucinations, confusion, somnolence, insomnia, dystonia, paresthesia, depression, anxiety, tremor, akinesia, extrapyramidal syndrome, abnormal gait, abnormal dreams, incoordination, psychosis, personality disorder, nervousness, choreoathetosis, amnesia, paranoid reaction, abnormal thinking; *Infrequent:* akathisia, neuropathy, neuralgia, hypertonia, delusion, convulsion, libido increased, euphoria, emotional lability, libido decreased, vertigo, myoclonus, coma, apathy, paralysis, neurosis, hyperkinesia, ataxia, acute brain syndrome, torticollis, meningitis, manic reaction, hypokinesia, hostility, agitation, hypotonia; *Rare:* stupor, neuritis, intracranial hypertension, hemiplegia, facial paralysis, brain edema, myelitis, hallucinations and confusion after abrupt discontinuation.

Respiratory System —*Frequent:* rhinitis, dyspnea, pneumonia, pharyngitis, cough increased; *Infrequent:* epistaxis, hiccup, sinusitis, bronchitis, voice alteration, hemoptysis, asthma, lung edema, pleural effusion, laryngitis, emphysema, apnea, hyperventilation; *Rare:* pneumothorax, lung fibrosis, larynx edema, hypoxia, hypoventilation, hemothorax, carcinoma of lung.

Skin and Appendages System —*Frequent:* sweating, rash; *Infrequent:* skin discoloration, pruritus, acne, skin ulcer, alopecia, dry skin, skin carcinoma, seborrhea, hirsutism, herpes simplex, eczema, fungal dermatitis, herpes zoster; *Rare:* vesiculobullous rash, subcutaneous nodule, skin nodule, skin benign neoplasm, lichenoid dermatitis.

Special Senses System —*Frequent:* diplopia; *Infrequent:* otitis media, conjunctivitis, tinnitus, deafness, taste perversion, ear pain, eye pain, glaucoma, eye hemorrhage, photophobia, visual field defect; *Rare:* blindness, cataract, retinal detachment, retinal vascular disorder.

Urogenital System —*Frequent:* urinary tract infection, urinary frequency, urinary incontinence, hematuria, dysmenorrhea; *Infrequent:* dysuria, breast pain, menorrhagia, impotence, cystitis, urinary retention, abortion, vaginal hemorrhage, vaginitis, priapism, kidney calculus, fibrocystic breast, lactation, uterine hemorrhage, urolithiasis, salpingitis, pyuria, metrorrhagia, menopause, kidney failure, breast carcinoma, cervical carcinoma; *Rare:* amenorrhea, bladder carcinoma, breast engorgement, epididymitis, hypogonadism, leukorrhea, nephrosis, pyelonephritis, urethral pain, uricaciduria, withdrawal bleeding.

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Early Therapy for Parkinson's Disease

To the Editor.—We read with interest the article by Elizan et al in the January issue of the ARCHIVES.[1] The authors suggest that the early combination of selegiline and levodopa initiated at the "earliest clinical expression of the disease process" seems a most reasonable approach. They base this suggestion on their observation that patients receiving selegiline alone experience a dramatic improvement in parkinsonian score following the addition of levodopa (Sinemet). As selegiline alone provides little or no symptomatic benefit as monotherapy in early Parkinson's disease,[2] it is not surprising that a significant symptomatic response was observed with the addition of levodopa. As the authors point out, it is not known how the response to levodopa and selegiline compares with that which could be achieved with levodopa alone, a dopamine agonist alone, or the combination of selegiline and a dopamine agonist.

The rationale for the use of selegiline in patients with early Parkinson's disease is that it may slow disease progression by diminishing the accumulation of free radicals associated with the oxidative metabolism of dopamine.[2] However, selegiline does not completely prevent the oxidation of dopamine, which may also undergo auto-oxidation or metabolism by the monoamine oxidase type A inhibitor. Therefore, levodopa administration, by way of its metabolism to dopamine, may continue to promote free radical production despite concurrent selegiline therapy.[3] If oxidation reactions and free radical formation are important in the pathogenesis of Parkinson's disease, it may be best to minimize the cumulative dose of levodopa employed over the course of the disease. This can be accomplished by (1) using selegiline therapy to delay the need for the symptomatic therapy, (2) initiating symptomatic therapy with a dopamine agonist that does not undergo oxidative metabolism, and (3) administering levodopa as an adjunct when satisfactory symptomatic benefit cannot be obtained with selegiline and a dopamine agonist alone. The use of levodopa as part of combination therapy with a dopamine agonist and selegiline should permit clinical benefit to be obtained with a lower dose than if it were used alone. This strategy would provide symptomatic control while minimizing the cumulative levodopa dose and the potential for levodopa-induced oxidative stress. Prospective controlled clinical trials to evaluate this approach are necessary.

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2. Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med.* 1989;321:1364-1371.
3. Olanow CW. Oxidation reactions in Parkinson's disease. *Neurology.* 1990;40:32-37.

In Reply.—We thank Hauser and Olanow for their comments and appreciate the various therapeutic strategies that they propose and which have been detailed in a previous publication.[1] Since their suggestions rely heavily on the results of the DATATOP study,[2,3] a comment on its design and interpretation is in order. DATATOP was designed as a clinical trial to test the intriguing hypothesis (originally suggested by Birkmayer et al[4] in 1985) that long-term monoamine oxidase type B (MAO-B) inhibition with the drug, selegiline (L-deprenyl), will provide a "protective" effect on nigral degeneration and *slow* the progression of Parkinson's disease (PD). To date, this hypothesis remains *unproven.* The DATATOP results demonstrate an effect on the clinical status of treated patients compared with untreated control subjects receiving no active symptomatic treatment of any kind. The delay in the *need for levodopa* (the authors' end point) in the selegiline-treated patients compared with the untreated control subjects was interpreted by the authors as reflecting a delay in the underlying disease progression (hence, "protective" rather than "symptomatic"). The latter interpretation assumes that the observed effect of the drug has a fundamental *causal* relationship to the disease process, which may or may not, in fact, exist. Or, alternatively, the observed effect was interpreted as proving the hypothesis that generated it in the first place. Moreover, it was not clear that the design of the study as actually performed permitted a distinction between "symptomatic" and "protective" explanation for the need for levodopa.

We had elected to define clinical progression in de novo cases of Parkinson's disease[5] as the emergence of *new* signs and symptoms, and/or the demonstrable *worsening* of those previously present, after the start of selegiline monotherapy. We found that selegiline by itself failed to avoid either of these and that it had only a modest effect as primary symptomatic therapy in early PD.[5] As an adjunct to long-term levodopa therapy in the more advanced disease,[6] a beneficial symptomatic response in a selected group of patients was observed, but no effect on disease outcome. We have been more inclined to view these data as not supporting (although not necessarily disproving) the hypothesis that MAO-B inhibition and other therapeutic strategies directed at reducing oxidative stress will slow the progression of PD.

One cannot disagree with Hauser and Olanow's recommendation that it is desirable to limit the daily dose of levodopa. We have advocated this practice for years, but for reasons that are substantially different from those that they propose. Our concern is not the cumulative effect of levodopa contributing to neuronal degeneration but, rather, the development of erratic pharmacological effects that occur after long-term usage. In part, we feel that this may relate to usage of a large daily dosage of levodopa required for symptom control. Selegiline allows for reduction of such dosage.

We have long been acutely aware of levodopa's hypothesized potential role in the pathogenesis of the disease itself,[7,8] especially if oxidative reactions and free radical formation were, indeed, involved in nigral cell death of PD. But, in fact, there are no conclusive data supporting the idea that levodopa, particularly that derived from an exogenous source, induces cell death even in experimental systems,[9-11] and, certainly, there are no such data in human PD. After more than 20 years of levodopa use in clinical practice, there is no convincing evidence in the literature that levodopa induces neuronal degeneration or accelerates the progression of PD, even after long-term administration of the drug. We do not, therefore, share Hauser and Olanow's concern that levodopa will contribute to the progression of the parkinsonian process, although we agree with them that the cumulative dose over time be held to a minimum.

Our article suggests that the early combination of selegiline and low-dose levodopa is appropriate as *initial therapy* in PD. The sentence quoted by the authors where we recommend the use of this regimen "at the earliest clinical expression of the disease process" can be construed as calling for the use of levodopa as soon as the diagnosis of PD is made. This was not our intent. The decision to start definitive therapy is based on the judicious evaluation of the individual patient's unique need for symptomatic relief, however "early" that might be.

The remarkable symptomatic reversal of parkinsonism with the addition of low-dose levodopa in deteriorating patients on selegiline monotherapy for an average of 13.8 months,[12] dramatizes, not so much the well-known levodopa effect, but the *paucity* of effect ("symptomatic" or "protective") of selegiline alone. The trial of early combination of low-dose levodopa and selegiline as initial therapy that we reported[12] obviously needed to be compared, as we indicated, with low-dose levodopa alone or combined with a dopamine agonist to attempt to clarify the role of each drug. A manuscript in preparation ("Levodopa Revisited: Low-Dose Levodopa Alone or Combined Early With a Monoamine Oxidase Inhibitor, Selegiline: The First 4 Years") will address the question of whether or not the use of selegiline does make a difference in altering the clinical course of parkinsonism as well as avoiding some of the long-term complicated pharmacological responses of levodopa.

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1. Olanow CW. Oxidation reactions in Parkinson's disease. *Arch Neurol*. 1990;40(suppl 3):32-37.
2. The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. *N Engl J Med*. 1989;321:1364-1371.
3. The Parkinson Study Group. DATATOP: a multicenter controlled clinical trial in early Parkinson's disease. *Arch Neurol*. 1989;46:1052-1060.
4. Birkmayer W, Knoll J, Riederer P, Hans V, Morton J. Improvement of life expectancy due to L-deprenyl addition to Madopar treatment in Parkinson's disease: a long-term study. *J Neurol Transm*. 1985;64:113-127.
5. Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline use to prevent progression of Parkinson's disease: experience in 22 de novo patients. *Arch Neurol*. 1989;46:1275-1279.
6. Elizan TS, Yahr MD, Moros DA, Mendoza MR, Pang S, Bodian CA. Selegiline as an adjunct to conventional levodopa therapy in Parkinson's disease: experience with this type B monoamine oxidase inhibitor in 200 patients. *Arch Neurol*. 1989;46:1280-1283.
7. Cohen G. Dembiec D, Mytilineou C, Heikkila RE. Oxygen radicals and the integrity of the nigrostriatal tract. In: Birkmayer W, Hornykiewicz O, eds. *Advances in Parkinsonism*. St Louis, Mo: Mosby–Year Book; 1976:251-257.
8. Yahr MD. Evaluation of long-term therapy in Parkinson's disease: mortality and therapeutic efficacy. In: Birkmayer W, Hornykiewicz O, eds. *Advances in Parkinsonism*. St Louis, Mo: Mosby–Year Book; 1976:435-443.
9. Hefti F, Melamed E, Bhawan J, Wurtman RI. Long-term administration of L-dopa does not damage dopaminergic neurons in the mouse. *Neurology*. 1981;31:1194-1195.
10. Melamed E. Role of the nigrostriatal dopaminergic neurons in mediating the effect of exogenous L-dopa in Parkinson's disease. *Mt Sinai J Med*. 1988;55:35-42.
11. Brannan T, Martinez-Tica J, Yahr MD. Effect of long-term L-dopa administration on striatal extracellular dopamine release. *Neurology*. 1991;45:596–598.
12. Elizan TS, Moros DA, Yahr MD. Early combination of selegiline and low-dose levodopa as initial symptomatic therapy in Parkinson's disease: experience in 26 patients receiving combined therapy for 26 months. *Arch Neurol*. 1991;48:31-34.

Trends in Parkinson's Disease Mortality in Italy

To the Editor.—In a recent issue of the Archives, Lilienfeld and colleagues[1] reported notable changes in age-specific mortality for Parkinson's disease (PD) during two decades (1962 through 1982) in the United States. The authors observed a decline in PD mortality rates among the middle aged and an increase in rates in the geriatric age group, both in whites and nonwhites and in both sexes. They concluded that these temporal changes, although possibly due to better case ascertainment and improved treatment of PD, may reflect a true rise in the incidence among the elderly, with some implication for the pathogenesis of the disease. Similar findings have been reported, but not discussed, by Li and colleagues[2] in England and Wales.

We have analyzed the mortality rates for PD in Italy in the period from 1957 through 1981 (*International Classification of Diseases* code 350.0 for the period from 1957 through 1966; 342.0 for the period from 1967 through 1978; and 332.0 for the period from 1979 through 1981). These data have been published yearly by the Italian Statistic Bureau, Rome. Only underlying causes are available.

The overall mortality rates, adjusted (for the 1971 Italian population), steadily increased during the period examined, both for men (1957 through 1961, 2.5/100 000 per year; for 1977 through 1981, 3.5/100 000 per year) and for women (1957 through 1961, 2.0/100 000 per year; for 1977-1981, 3.0/100 000 per year) (significance, $P < .001$). Furthermore, the following different trend was observed in the various age classes: the increase in mortality rates was evident among subjects older than 75 years of age, but a decrease was found among younger patients.

The cases were also analyzed by quinquennial birth cohorts: in both sexes, a progressive increase in mortality rates was found from the 1870 through 1874 cohort, with a maximum in the 1900 through 1904 cohort and a progressive decline in more recent cohorts. Interestingly, Brown and Knox[3] found a similar phenomenon in England and Wales during the period from 1943 through 1968, with a maximum in the 1895 through 1899 cohort. We feel that it is hard to ascribe these findings to methodological biases (such as better case ascertainment or modification in PD coding) or to the effect of new therapies that could cause delayed deaths (levodopa therapy was introduced in Italy in the early 1970s, while changes in mortality rates have been noted since 1960). On the contrary, these trends, observed in different geographical areas, seem to indicate that some cases of PD may have been caused by an environmental factor, possibly in the early decades of the 20th century, that had only a minimal or no effect after 1930. It would be useful to analyze the mortality rates reported in more recent years to confirm or deny the observed effect and also to analyze the variations in mortality in different geographical areas of the same country. Clearly, the definitive demonstration of this finding could give important support to the hypothesis that PD is caused by environmental or exogenous factors.

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1. Lilienfeld DE, Chan E, Ehland J, et al. Two decades of increasing mortality from Parkinson's disease among the US elderly. *Arch Neurol.* 1990;47:731-734.

2. Li T-M, Swash M, Alberman E. Morbidity and mortality in motor neuron disease: comparison with multiple sclerosis and Parkinson's disease: age and sex specific rates and cohort analyses. *J Neurol Neurosurg Psychiatry.* 1985;48:320-327.

3. Brown EL, Knox EG. Epidemiological approach to Parkinson's disease. *Lancet.* 1972;1:974-976.

A Commentary on Steroid Treatment in Multiple Sclerosis

To the Editor.—A number of studies have shown that pulsed therapy with high-dose intravenously administered methylprednisolone is usually effective during multiple sclerosis (MS) relapses. It has been hypothesized that a regimen of repeated pulses of intravenous methylprednisolone, not restricted to relapses but given at regular intervals during the years of disease activity, might be effective in preventing progression of the disease. It can, however, reliably be predicted that under these circumstances the frequency of adverse effects will rise and, therefore, the importance of assessing the exact benefits and risks of such a regimen has been stressed in a number of leading articles.[1-3] We recently performed a small, open, pilot study in which monthly pulses of methylprednisolone (500 mg intravenously) were given to patients with progressive MS. Ten patients with definite MS according to the Poser criteria were selected for the study. During the 12 months before entry into the study all of the patients had deteriorated at least two steps (ie, one full point) on the Kurtzke Expanded Disability Status Scale (EDSS). The main aim of the study was to investigate the safety of this long-term steroid regimen.

Serum glucose and creatinine concentrations were examined monthly. Serum calcium, phosphate, alkaline phosphatase, osteocalcin, and parathyroid hormone concentrations, and the urinary calcium/creatinine and hydroxyproline/creatinine ratios were determined every 3 months to study bone metabolism. An increase of these urinary ratios would be indicative of increased bone resorption. Bone mineral densities were measured quantitatively in the lumbar vertebral column with dual energy X-ray absorptiometry and in the radius with single photon absorptiometry every 3 months. Guidelines for the clinical use of bone mass measurements have been given by Johnston et al.[4] Very recently, the importance of bone density measurements in MS trials involving steroid treatment was stressed by Whitham et al.[5] Cortisol response to corticotropin was tested every 3 months to examine adrenal function: cortisol levels were measured both before and 30 minutes after the intravenous administration of 0.25 mg of synthetic 1-24-corticotropin (Synacthen, Organon, Holland), and both relative and absolute increases were analyzed (short corticotropin stimulation test). To document the clinical course Kurtzke's EDSS was determined monthly.

After a mean treatment duration of 9 months there were no signs of cushingoid appearance, behavioral changes, or hypertension in any of the patients. Two patients had to be treated with antibiotics for lower urinary tract infections; no serious infections occurred. The treatment was tolerated well, although seven of 10 patients suffered from insomnia the night after the infusion. All laboratory parameters are given in the Table. It is clear that no clinically significant changes were found during the course of the treatment. There was no loss of bone mass (as documented by dual energy X-ray absorptiometry and single photon absorptiometry), there were no changes in bone metabolism (as documented by serum calcium, phosphate, alkaline phosphatase, osteocalcin, and parathyroid hormone concentrations and 24-hour urine calcium/creatinine and hydroxyproline/creatinine ratios), and there was no indication of any suppression of adrenal function (as documented by the short corticotropin stimulation test). The mean Kurtzke EDSS was 5.8 at entry and 5.5, 5.9, and 6.2 after 3, 6, and 9 months of treatment, respectively, resulting in a mean increase of 0.4 after 9 months (mean increase in the corresponding period before treatment 0.9).

Our data convincingly demonstrate that our treatment regimen (monthly infusions of 500 mg of methylprednisolone) can be administered in MS patients without side effects for at least 9 months. The findings on the complete absence of any change in bone mineral density measurements after this treatment duration are of special significance. It has previously been indicated that corticoid-induced loss of bone mass occurs predominantly within the first 5 to 7 months of treatment, whereas during the subsequent stages only minor changes can be observed.[6] Evaluating the same parameters as we did, several groups have demonstrated the occurrence of a bone loss of about 10% due to conventional oral dosing steroid regimens with cumulative dosage and treatment duration being comparable to ours (for review see Lukert and Raisz[7]). The absence of adrenal insufficiency in our patients is also remarkable since in other studies it was found that conventional regimens of prednisone with a cumulative dosage comparable to ours can lead to suppression of adrenal

Mean Laboratory Parameters Obtained Before and During the Treatment*

		Months		
	Before Entry	3	6	9
	Serum			
Glucose, mmol/L	4.8	5.0	4.6	4.1
Creatinine, µmol/L	82	84	84	82
Alkaline phosphatase, U/L	60	62	63	61
Calcium, mmol/L	2.34	2.38	2.39	2.42
Phosphate, mmol/L	1.07	1.17	1.08	1.18
Osteocalcin, µg/L	4.1	4.1	4.2	4.2
Parathyroid hormone, pmol/L	1.8	2.2	2.2	2.1
Corticotropin test				
Relative increase, %	95	102	88	103
Absolute increase, nmol/L	367	383	339	417
	24-Hour Urine			
Hp/Cr ratio, µmol/mmol	29.0	25.8	20.4	23.1
Ca/Cr ratio, mmol/mmol	0.47	0.51	0.37	0.43
	Bone Mineral Density			
Lumbar vertebrae, g/cm² (DEXA)	0.92	0.92	0.93	0.95
Radius, mg/cm² (SPA)	574	562	565	565

*Hp/Cr ratio indicates hydroxyproline/creatinine ratio; Ca/Cr ratio, calcium/creatinine ratio; DEXA, dual energy X-ray absorptiometry; and SPA, single photon absorptiometry.

function after only 2 to 3 weeks.[8,9]

Based on our findings, a large controlled study can be justified to evaluate the efficacy of this regimen of repeated pulses of intravenous methylprednisolone in the treatment of MS, either in the prevention of relapses or in preventing progression of the disease.

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1. Troiano R, Cook SD, Cowling PC. Steroid therapy in multiple sclerosis: point of view. *Arch Neurol.* 1987;44:803-807.
2. Compston A. Methylprednisolone and multiple sclerosis. *Arch Neurol.* 1988;45:669-670.
3. Menken M. Consensus and controversy in neurologic practice: the case of steroid treatment in multiple sclerosis. *Arch Neurol.* 1989;46:322.
4. Johnston CC, Melton LJ, Lindsay R, Eddy DM. Clinical indications for bone mass measurements. *J Bone Mineral Res.* 1989;4(suppl 2):1-28.
5. Whitham RH, Schaumann BA, McClung M, Perry B, Gehling AM, Bourdette D. Premature osteoporosis in multiple sclerosis: implications for corticosteroid therapy. *Neurology.* 1990;40(suppl 1):284.
6. LoCascio V, Bonnuci E, Imbimbo B, et al. Bone loss in response to long term glucocorticoid therapy. *Bone Mineral.* 1990;8:39-51.
7. Lukert BP, Raisz LG. Glucocorticoid induced osteoporosis: pathogenesis and management. *Ann Intern Med.* 1990;112:352-364.
8. Axerold L. Glucocorticoid therapy. *Medicine.* 1976;55:39-66.
9. Christy NP. Principles of systemic corticosteroid therapy in nonendocrine disease. In: Krieger DT, Bardin CW, eds. *Current Therapy in Endocrinology and Metabolism.* Philadelphia, Pa: BC Decker; 1985:366-375.

Epidural Steroids Are Safe and Effective When Given Appropriately

To the Editor.—We read with interest Nelson's[1] most recent attack on the use of intraspinal steroids. It appears that Nelson is continuing his relentless crusade to banish the use of epidural steroids, a crusade based, as usual, more on an emotional than on a scientific basis.

Initially it appears that the 19 references in his letter to the editor[1] would strongly support his viewpoint. However, on closer evaluation, one realizes that 14 of those 19 references are Nelson's articles, many of which are simply letters to the editor or lectures to others rehashing the same material.

The majority of the references discounting the use of intraspinal steroids address the intrathecal use. In addition, most of the complications encountered by Nelson, or quoted by him, occurred in patients with another significant neurologic disease process, ie, multiple sclerosis. And, when Nelson refers to Bernat's article[2] regarding a complication from intrathecal administration, he fails to mention the fact that this case was a subdural rather than subarachnoid injection, and he fails to refer to Bernat's later review article[3] when he emphasizes that the epidural route appears to be relatively safe.

It is significant to note that in Nelson's letter he refers to *60 Minutes Australia* and *A Current Affair Australia.* Although we are sure that these are interesting programs for public consumption, they would hardly qualify as reputable scientific references. He goes on to state that Upjohn altered its package insert in this country in 1989 to warn against epidural injections of Depo-Medrol, but on close examination of the most recent package insert, we can find no such warning.

Most anesthesiologists who administer epidural steroids agree that it is inadvisable to inject the steroid intrathecally, although even this is based more on medicolegal than on medical grounds. However, when administered appropriately, epidural steroid injections have an excellent safety record. In our clinic, Brooke Army Medical Center, Fort Sam Houston, Tex, we have administered over 5000 epidural steroid injections over the last 10 years without a single known case of arachnoiditis. Others[4-9] have reported a similar safety record.

Obviously, there are risks associated with any invasive procedure; and while complications are rare, Nelson has outlined those that have been reported very well. However, in medicine we must weigh the risks of any treatment against the benefits and compare that risk-benefit ratio with the alternatives; the alternatives to epidural steroids include bedrest, physical therapy, chronic drugadministration, and surgery, and in many instances these alternatives carry even a greater risk than epidural steroids and may, in addition, lead to further cost and loss of income.

Although we are unaware of how and to whom epidural steroids are administered in Australia, in this country we hear only a "ground swell" of patient appreciation for the relief obtained from our patients. When administered with proper expertise, with appropriate patient selection, with the proper dosage and when the injections are limited in number, we believe that the administration of epidural steroids will continue to be a safe and effective therapy for certain neurologic derangements. All of the above criteria are well outlined by Benzon[10] in his review article. We further believe that it is time for Nelson to stop beating a dead horse; if he continues and if we allow him to create the hysteria in the professional press similar to that generated in Australia in the lay press, we will only deprive our patients of a very important therapeutic modality.

The opinions or assertions contained herein are the private views of the authors and are not to be construed as reflecting the views of the Department of the Army or the Department of Defense.

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2. Bernat JL, Sadowsky CH, Vincent FM, Nordgren RE, Margolis G. A complication of intrathecal administration of Depo-Medrol for multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1976;39:1124-1128.
3. Bernat JL. Intraspinal steroid therapy. *Neurology.* 1981;31:168-171.
4. Delaney TJ, Rowlingson JC, Carron H, Butler A. Epidural steroid effect on nerves and meninges. *Anesth Analg.* 1980;59:610-614.
5. Abram SE. Perceived dangers from intraspinal steroid injections. *Arch Neurol.* 1989;46:719-720.
6. Goebert HW, Jallo SJ, Gardner WJ, et al. Sciatica: treatment with epidural injections of procaine and hydrocortisone. *Cleve Clin Q.* 1960;27:191-197.
7. Swerdlow M, Sayle-Creer W. The use of extradural injections in the relief of lumbo-sciatic pain. *Anaesthesia.* 1970;25:128.
8. Winnie AP, Hartman JT, Meyers HL, et al. Pain clinic II: intradural and extradural corticosteroids for sciatica. *Anesth Analg.* 1972;51:990-999.
9. Dilke TFW, Burry HC, Grahame R. Extradural corticosteroid injection in management of lumbar nerve root compression. *BMJ.* 1973;2:635-637.
10. Benzon HT. Epidural steroid injections for low back pain and lumbosacral radiculopathy. *Pain.* 1986;24:277-295.

In Reply.—Controversy concerning the intraspinal use of methylprednisolone acetate (Depo-Medrol, Upjohn Co, Kalamazoo, Mich) began in 1970, naturally leading to a number of editors' invitations (as here) for me to reply to adverse opinions.

The manufacturer issued its first warning concerning epidural use in the United States in October 1989 and in Australia in November 1990. Because the drug has a 36-month shelf life, Strong et al may not have yet seen the new package-insert pamphlet, and the

Upjohn Company plans no general "Dear Doctor" letter. Six months after the warning against epidural use in the United States was first printed, I was notified that about 150 patients in Western Australia claimed complications from epidural steroid therapy.[1] Why such a large number of patients in one Australian state spontaneously reported their symptoms without media induction or medical publications is unknown. Contrary to Strong et al, I believe that serious complications from *intrathecal* steroid therapy bear directly on potential dangers from *epidural* injections. Second, I believe that animal research has been inadequate. Two previous publications[1,2] summarized scientific conflicts attendant to intrathecal steroid therapy that began in 1960 and concerning epidural therapy that began around 1975. Thousands of intrathecal injections were given over the last 30 years in attempts to treat low back pain, disk disease, the failed back syndrome, as well as multiple sclerosis.[3-9] By far, the drug has been prescribed most frequently for nondescript back pain and sciatica, a 1960 regimen using methylprednisolone acetate, introduced by Sehgal and Gardner[6,7] and Sehgal et al.[8,9]

The steroid compound known to be neurotoxic contains approximately 30 mg of polyethylene glycol per milliliter.[10-13] Prior to human trials, Sehgal and colleagues[6-9] published no original animal research in which the above steroid compound was used, referring instead to works done by others who studied cortisone or hydrocortisone injected intrathecally. No subhuman primates have ever been tested. After numerous neurological complications were reported, the Upjohn Company issued their first warnings against intrathecal use in 1979 and 1980. Simultaneously, similar disturbing findings were published by three different groups of neuroradiologists[14-16] who together reported the occurrence of almost 100% arachnoiditis in 86 patients, even from a single small intrathecal dose of methylprednisolone acetate. Most neuroscientists thereafter abandoned its use, but anesthesiologists were already publishing that epidural therapy was safe and effective. An often quoted 1972 review article by Winnie et al[17] mentioned the safety of intraspinal steroid therapy by referencing the earlier work by Sehgal et al,[9] who—as explained above—apparently never did animal research using methylprednisolone acetate. Apparently relying on those previous reports, Winnie et al[17] (as did Sehgal and Gardner[6,7] and Sehgal et al[8,9]) only referred back to animal experiments done in 1955 by others who used cortisone and hydrocortisone—never methylprednisolone acetate.

In 1980, Delaney et al[18] reported that triamcinolone acetate, administered to only 10 cats, was safe when given epidurally. However, I note that animals given the vehicle alone demonstrated more meningeal changes. It was surprising to me that not until 1990 was methylprednisolone acetate finally tested on 12 rabbits by Cicala et al[19] who killed the animals on days 4 through 10 and reported no meningeal changes. This short-term research on such a minuscule series of small animals is inadequate to reassure human safety. Studies on large subhuman primates are obviously needed.

How often do epidural injections result in inadvertent spinal taps (thus virtually guaranteeing arachnoiditis)? Spinal fluid is obtained in 0.5% to 2.5% of routine epidural procedures.[20] Anesthesiology trainees have unsuccessful placements in 5%.[21] An experienced operator treating patients with spinal disease was unsuccessful in 6%.[22] Patients in pain clinics present technical problems to the operator because the "failed back" offers cicatricial obstructions to epidural catheters, resulting in inadvertent spinal taps. Even subdural placements can result in serious complications.

I respectfully request Strong et al to again read my last letter to the editor in the ARCHIVES[1] to which they object. Beginning at sentence 12, I described studies by Bernat et al[10] and Bernat[11] correctly when I wrote that a "second sac" was formed from an inadvertent subdural injection that spread intracranially. There will soon be a strong movement to abandon epidural therapy with methylprednisone acetate based on just published study by Johnson et al[23] from Australia. Following up on the original 1984 study by Roche[16] (in which he reported on radiographically proven arachnoiditis from intrathecal and epidural steroids), the new review disclosed that 20% went on to develop clinical signs and symptoms. Finally, the recent new edition of *Anesthesia*,[24] edited by Miller, summarized the present uncertain status of epidural steroid therapy by stating that such therapy is frequently ineffective for the "failed back" and by concluding, "Although this therapy is widely used and epidural administration seems relatively safe, use of steroids in a polyethylene glycol vehicle is probably not advisable."[24]

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1. Nelson DA. Further warnings from Australia concerning intraspinal steroids. *Arch Neurol*. 1991;48:259.
2. Nelson DA. Dangers from methylprednisolone acetate therapy by intraspinal injection. *Arch Neurol*. 1988;45:804-806.
3. Boines GJ. Remissions in multiple sclerosis following intrathecal methylprednisolone acetate. *Del Med J*. 1961;33:230-235.
4. Boines GJ. Predictable remissions in multiple sclerosis. *Del Med J*. 1963;35:200-203.
5. Boines GJ. Erratic persistence of intrathecally injected methylprednisolone acetate. *Del Med J*. 1964;36:210-212.
6. Sehgal AD, Gardner WJ. Corticosteroids administered intradurally for relief of sciatica. *Cleve Clin Q*. 1960;27:198-201.
7. Sehgal AD, Gardner WJ. Place of intrathecal methylprednisolone acetate in neurological disorders. *Trans Am Neurol Assoc*. 1963;88:275-276.
8. Sehgal AD, Gardner WJ, Dohn DF. Pantopaque arachnoiditis treatment with subarachnoid injection of corticosteroids. *Cleve Clin J Med*. 1962;29:177-178.
9. Sehgal AD, Tweed DE, Gardner WJ, Foote MK. Laboratory studies after intrathecal corticosteroids: determination of corticosteroids in plasma and cerebrospinal fluid. *Arch Neurol*. 1963;9:64-68.
10. Bernat JL, Sadowsky CH, Vincent FM, et al. Sclerosing pachymeningitis, a complication of intrathecal administration of Depo-Medrol for multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 1976;39:1124-1128.
11. Bernat JL. Intraspinal steroid therapy. *Neurology*. 1981;31:169-171.
12. Selby R. Depo-Medrol. *Neurosurgery*. 1983;12:591.
13. Selby R. Complications from Depo-Medrol. *Surg Neurol*. 1983;19:393-394.
14. Dullerud R, Morland TJ. Adhesive arachnoiditis after lumbar radiculography with Dimer-X and Depo-Medrol. *Radiology*. 1976;119:153-155.
15. Duchesneau PM, Weinstein MA, Wesolowski DP. Lumbar arachnoiditis: long term effects of intrathecal Depo-Medrol. *Neuroradiology*. 1978;15:244.
16. Roche J. Steroid-induced arachnoiditis. *Med J Aust*. 1984;140:281-284.
17. Winnie AP, Hartman JT, Meyers HL, Ramamurthy S, Barangan V. Pain clinic, II: intradural and extradural corticosteroids for sciatica. *Anesth Analg*. 1972;51:990-999.
18. Delaney TJ, Rowlingson JC, Carron H, Butler A. Epidural steroid effects on nerves and meninges. *Anesth Analg*. 1980;58:610-614.
19. Cicala RS, Turner R, Morgan BS, Henley R, Wong R, Evans JL. Methylprednisolone acetate does not cause inflammatory changes in the epidural space. *Anesth Analg*. 1990;72:556-558.
20. Albright GA. *Anesthesia in Obstetrics: Maternal, Fetal and Neonatal Aspects*. Menlo Park, Calif: Addison-Wesley Publishing Co; 1978:224-226.
21. Abram SE. Perceived dangers from intraspinal steroid injections. *Arch Neurol*. 1989;46:719-720.
22. White AH. Injection techniques for the diagnosis and treatment of low back pain. *Orthop Clin North Am*. 1983;14:326-328.
23. Johnson A, Ryan MD, Roche J. Depo-Medrol and myelographic arachnoiditis. *Med J Aust*. 1991;155:18-20.
24. Murphy TM. Chronic pain. In: Miller RD, ed. *Anesthesia*. 3rd ed. New York, NY: Churchill Livingstone Inc; 1990:1940.

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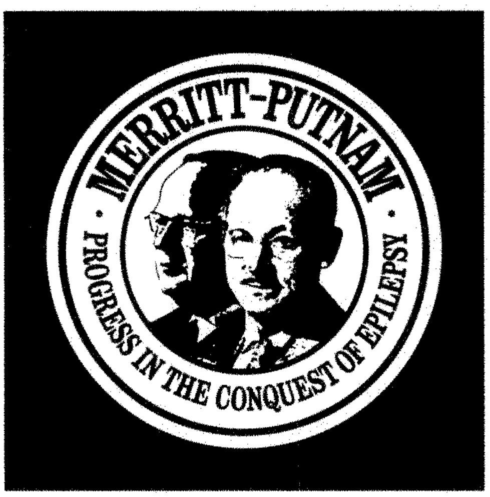
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Clinical Correlates of White-Matter Changes on Magnetic Resonance Imaging Scans of the Brain

Thomas R. Mirsen, MD; Donald H. Lee, DM; Cindy J. Wong, MSc;
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• We report our observations on the clinical and radiologic correlates of changes in cerebral white matter based on 94 subjects undergoing magnetic resonance imaging in a prospective study of dementia. Periventricular hyperintensity occurred twice as often in patients with Alzheimer's disease as in healthy control subjects. Within the control group, the presence of periventricular hyperintensity correlated significantly with one measure of cerebral atrophy and with the presence of changes in the adjoining deep white matter. The significance of white-matter changes distinct from the ventricles (leuko-araiosis) remains unsettled. Leuko-araiosis on the magnetic resonance imaging scan, unlike its correlate on the computed tomographic scan, was not shown to relate to cognitive decline or to the presence of focal abnormalities on neurologic examination. This is likely to reflect the heterogeneity of the changes detected with magnetic resonance imaging and their limited extent in our subjects.

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Magnetic resonance imaging (MRI) permits the identification of subtle changes in the white matter of the brain.[1-3] Various investigators have reported a high prevalence of white-matter changes on T_2-weighted images,[1,2,4-10] especially in subjects with cerebrovascular disease.[1,2,4,5,7,8] We distinguish between periventricular hyperintensity (PVH) (Fig 1) and changes distant from the ventricles (Fig 2), or leuko-araiosis (L-A).[11]

SIGNIFICANCE OF L-A AND PVH

Leuko-araiosis appears infrequently on MRI scans[4,6,12] in young subjects and occurs more commonly[4,12] with age. It may appear often[5,12] and may be extensive[12] in Alzheimer's disease (AD).[5,12] However, our interpretation of the data of Erkinjuntti et al[13] suggests that severe changes are rare. Computed tomographic studies[14-16] reveal an association between similar lucencies and AD. No link exists between L-A on MRI scans and cognitive dysfunction, whether in AD,[12,13,17] among healthy control subjects,[18-20] in multi-infarct dementia (MID),[12] or in unselected subjects.[4] This contrasts with the relationship demonstrated between mental decline and L-A on CT scans.[21,22] Gait disturbance does relate to L-A on MRI scans of healthy subjects,[18] as previously shown for CT changes.[21] Leuko-araiosis appears on MRI scans in 64%[23] to 100%[12,13] of subjects with MID. Its effect on this condition remains unknown.

Periventricular hyperintensity is more prevalent than L-A in older[8-10,12] and possibly in younger[6,10,12] subjects. Its frequency casts doubt on its importance. The reported percentage of patients with AD who exhibit PVH varies from 44% to 100%.[12,13,17,23] One study[23] noted PVH in 71% of patients with MID, and other studies[12,13] noted PVH in 100% of patients with MID.

The incomplete knowledge regarding these white-matter changes results in part from variations among the existing studies.[*] Some rest primarily on preexisting radiologic data[7-10,35,41,45,47] or on pathologic findings.[†] The clinical information presented may be retrospective.[7-9,35,41] Given studies involve unselected subjects[1,4,7,10,41]; certain studies[5,17,26,29] involve modest numbers. Some investigators[5,6,20,32,33,43] report the prevalence of white-matter changes in various diagnostic groups; other investigators[‡] also delineate their extent. Most of these latter investigators[12,13,17-20,23,39,40,48] address the effect of these lesions on cognition. Many reports[12,13,18,20,39,40,48] include a neuropsychologic evaluation; some[17,23] rely on screening tools. Other studies[4,7-9,20,32,43,44] primarily examine the relationship between vascular risk factors and white-matter changes. Few[6,9,20,39,41] attend to focal neurologic findings. Other studies deal with the correlation between T_1[25,30,31] and T_2[26] measurements in the white matter and dementia.

No study has determined with certainty the contribution of white-matter changes seen on MRI scans to the severity of AD or MID. Bowen et al[12] stated that patients with AD exhibit more extensive L-A than do control subjects. However, Leys et al[17] found no effect of L-A or PVH on cognition in AD. Other studies[23,40] examined the effect of L-A and of PVH on cognition in cohorts of subjects with diverse diagnoses. Many studies have provided instructive infor-

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[*] References 1, 4-10, 12, 13, 17-20, 23-48.

[†] References 24, 27, 28, 34, 36, 37, 42, 46, 47.

[‡] References 12, 13, 17-19, 23, 29, 39, 48.

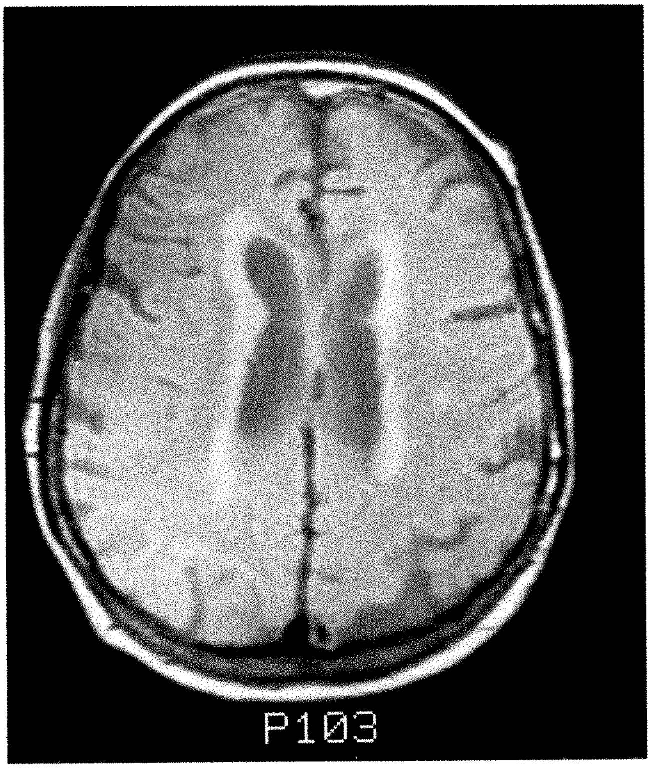

Fig 1.—Periventricular hyperintensity on a proton-density magnetic resonance imaging scan.

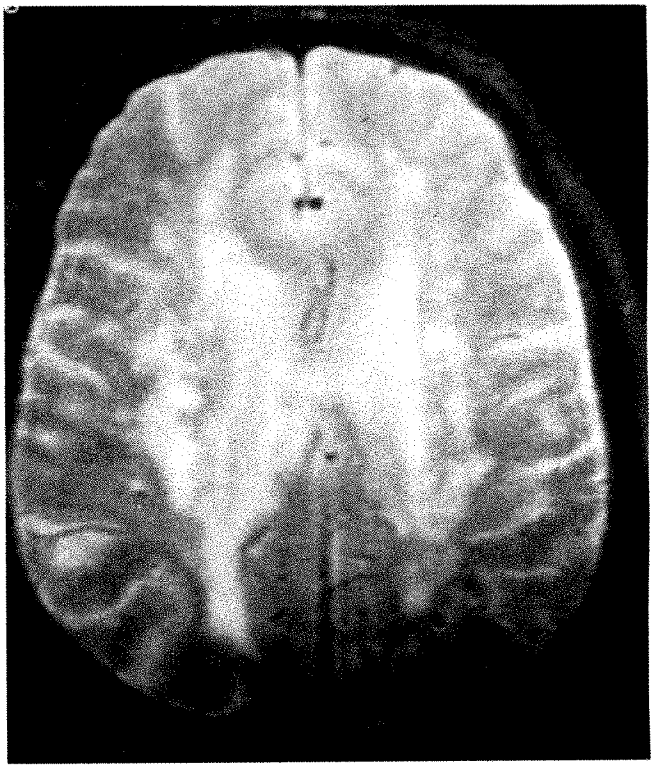

Fig 2.—Leuko-araiosis on a T_2-weighted magnetic resonance imaging scan.

mation, but it is difficult to control the numerous factors that influence the data.

Previous reports[15,21,22,38] from a large prospective study of dementia have examined the prevalence, clinical meaning, and probable cause of white-matter lucencies on CT scans. The acquisition of an MRI scanner and the presence of a pool of patients and control subjects who were examined systematically has made possible similar analyses based on MRI findings.

PATIENTS AND METHODS

The Dementia Study of the University of Western Ontario, London, which began in 1978, involves prospective clinical and radiologic examination of healthy volunteers and patients referred for the investigation of dementia. Participants in the study underwent standardized evaluation, performed from July 1985 to July 1986 by one physician (J.F.D.) and for the next 3 years by one neurologist (T.R.M.), confirmed in both cases by another neurologist (V.C.H.). Laboratory studies included a complete blood count; determinations of serum glucose, electrolyte, urea, creatinine, vitamin B_{12}, and folate levels; a liver profile; measurements of thyroid functions (including thyroid-stimulating hormone); and VDRL testing. Subjects initially underwent CT of the head. Magnetic resonance imaging scans have been obtained since November 1986, and electroencephalograms are obtained yearly. All testable subjects undergo psychometry at 6-month intervals, with the Extended Scale for Dementia (ESD),[49] with a sensitivity of 89% and a specificity of 96% in the identification of dementia.[50]

The physicians apply the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, criteria[51] in diagnosis and use the Ischemic Score[52] to distinguish among AD, "mixed" dementia, and MID. Our diagnosis of AD has a sensitivity of 87% and a specificity of 78%.[53]

Magnetic resonance imaging scans were obtained with a 1.5-T unit (Signa, General Electric, Milwaukee, Wis). They were originally obtained as follows: in the sagittal plane, with a 24-cm field of view (FOV), a repetition time (TR) of 500 milliseconds and an echo time (TE) of 20 milliseconds, taking 5-mm sections 1 mm apart. Axial cuts involved a 20- to 24-cm FOV, a TR of 2000 milliseconds and TEs of 35 and 70 milliseconds, taking 5-mm sections with 2.5-mm gaps. Coronal cuts involved a 16-cm FOV, a TR of 2000 milliseconds, and TEs of 20, 40, 60, and 80 milliseconds, as well as a TR of 600 milliseconds and a TE of 20 milliseconds, taking 3-mm sections 3 mm apart.

Later, the sagittal TRs were changed to 400 milliseconds, and axial cuts were performed with a 20-cm FOV, a TR of 2500 milliseconds, and TEs of 30 and 70 milliseconds, with flow compensation and 5-mm contiguous sections. The coronal cuts involved a 20-cm FOV, a TR of 500 milliseconds, and a TE of 20 milliseconds, with a 5-mm section thickness.

Two neuroradiologists (A.J.F. and D.H.L.) independently analyzed the MRI scans obtained for the Dementia Study between November 1986 and May 1988, without knowledge of clinical diagnoses, for the presence of L-A, PVH, sulcal widening, ventricular dilatation, and infarction. Periventricular hyperintensity (Fig 1) refers to areas of heightened intensity at the margins of the lateral ventricles. We distinguish between PVH and L-A because some PVH may appear normally,[47] while L-A may represent infarction[24,27,28,46] or demyelination and gliosis.[24,28,42] Periventricular hyperintensity was classified as absent or present in each hemisphere separately; more elaborate classification proved unreliable because of discordance between observations made on coronal and axial sections. Most work has relied on axial views.[§] Where other cuts were taken,[1,5,12,19,39,41,48] assessments of severity apparently rested primarily on the axial cuts, although not in some instances.[12,39] We deemed small areas of hyperintensity at the frontal or occipital horns of the lateral ventricles as normal.[47] Leuko-araiosis was rated in each hemisphere according to the number and severity of lesions. Absence of lesions received a grade of 0, one or two focal lesions received a grade of 1, three to five lesions received a grade of 2, and more than five lesions received a grade of 3; confluent lesions received a grade of 4. Whether the changes were relatively superficial ("subcortical"), "deep" (within 2 mm of the ventricular border but separated by a strip of normal-appearing brain), or both was also noted. If the radiologists disagreed, they reviewed the appropriate film together. They agreed initially about the presence of L-A in 88% of cases, about its extent in 56% of cases, and about the site involved in 71% of cases; they agreed as to the presence of PVH in 76% of instances. These data refer to the right hemisphere; the left hemisphere yielded comparable results.

[§] References 6, 10, 13, 17, 18, 20, 32, 37, 40, 44, 47.

Sulcal widening, scored from 0 to 5 on a severity scale, was examined in five zones on either side: sylvian and retrosylvian areas, the high and low convexities, and the perimesencephalic cistern. The mean of all the values provided the sulcus widening score.

Ventricular dilatation likewise received a score between 0 and 5. It was assessed in two parts of the lateral ventricles—the temporal horns and the bodies together with the frontal horns—as well as in the third and fourth ventricles.

SUBJECTS AND METHODS

We reviewed information concerning 102 subjects from the Dementia Study who underwent MRI scanning between November 1986 and August 1988. Eight subjects were excluded because of doubt as to the presence or type of dementia. The remaining 94 subjects included 44 subjects suffering from dementia and 24 control subjects who underwent full investigation in the study within 2 years of MRI scanning. The remaining 26 subjects were control subjects examined before the introduction of a standardized neurologic evaluation form. However, their ESD scores remained in the normal range (>220) when they returned for MRI scanning.

We determined the prevalence of PVH and L-A, whether deep, subcortical, or both, and the severity of L-A in the various diagnostic groups (AD, mixed dementia, MID, and healthy control subjects). We assessed the relationship between PVH and age or sex among our subjects. We determined whether the presence of PVH or of either type of L-A bore a relation to the presence of atrophy, as measured by the sulcus widening score and by lateral ventricular enlargement. Lastly, we analyzed whether PVH and either variety of L-A appeared together. In all instances, the two hemispheres were assessed separately. All analyses, except for the last, were conducted with both the inclusion and exclusion of subjects with radiologically defined infarcts. Periventricular hyperintensity could not be assessed in three and L-A in two of the 94 scans because of poor image quality.

The effects of PVH and both types of L-A on the ESD score were assessed among 28 patients with AD and 39 control subjects independently. These were the persons with these diagnoses among the 81 of the original 94 subjects who had undergone psychometric evaluation within 6 months of MRI scanning. The radiologic findings were judged separately in each hemisphere.

To determine whether the presence of any focal neurologic finding correlated with the presence of PVH or of a type of L-A, we selected a further subset of 50 subjects. These subjects were those whose neurologic examinations were performed within 1 year of the MRI scanning. From these 50 subjects, we excluded four with MID, two with mixed dementia, and one with an uncertain diagnosis. This left 43 subjects remaining: 20 with AD, five with mixed dementia, and 18 healthy control subjects. The 43 subjects included those persons with mixed dementia according to the Ischemic Score but no evidence of cerebral infarction, as well as three AD patients and two control subjects with infarcts seen on the MRI scan. Exclusion of such persons would, by eliminating subjects with focal neurologic signs, reduce the chances of detecting an association between such signs and white-matter changes. We also kept the patients with mixed dementia in the analysis because they may have suffered from AD. Our diagnostic criteria maximize the purity of the AD group, so that some patients who prove to have AD on pathologic examination are classified clinically as having mixed dementia.[53]

The findings assessed appear in Table 1. Some were excluded from further consideration because they occurred in less than 5% of subjects. Most were compared with radiologic findings in the contralateral hemisphere, but some (dyspraxia, dysarthria, and primitive reflexes) were compared with findings on either side.

STATISTICAL ANALYSIS

Pearson correlation coefficients and χ^2 values were calculated as indicated between PVH or L-A and relevant variables. Fisher's Exact Test was used when cell sizes were small. The association between the severity of L-A and the presence of other characteristics, such as PVH, was examined with Kendall's τ statistic. The atrophy measures and the ESD score were compared with the Student t test. Partial correlations were computed to examine the prevalence of PVH in control and AD groups while controlling for age and sex. All P values are based on two-tailed tests.

RESULTS

The 94 study subjects included 30 patients with AD, nine with mixed dementia, and four with MID, 50 control subjects, and a man suspected to have encephalitis. The controls included 23 men and 27 women (mean [SD] age, 70.1 [9.7] years), six of whom exhibited small cerebral infarcts on the MRI scan. The demented subjects included 23 men and 21 women (mean [SD] age, 72.2 [7.8] years). The patients with AD included 13 men and 17 women (mean [SD] age, 72.8 [6.9] years), three of whom exhibited cerebral infarcts on the MRI scan. The subjects with mixed dementia included five men and four women (mean [SD] age, 70.7 [11.0] years). The patients with MID included four men (mean [SD] age, 69.9 [8.0] years).

Both PVH and L-A appeared to the same extent in the two hemispheres. Data are given only for the right side, except where a difference between hemispheres requires mention. On three scans, PVH could not be interpreted. Thus, it appeared in the right hemisphere in 18 (64%) of 28 patients with AD, in three of eight patients with mixed dementia, and in three of four patients with MID, as well as in 15 (30%) of the 50 control subjects. When subjects with infarcts seen on MRI scans were excluded, the prevalence for the right hemisphere in the AD group changed from 64% to 60% and in the controls from 30% to 31%. Whether subjects with infarcts are included or excluded, the difference in prevalence between the two groups is significant (χ^2, $P=.003$ and $P=.019$, respectively). This remains the case after controlling for age and sex ($P=.006$, if cases with infarcts are included; $P=.024$, if cases with infarcts are excluded). Examination of the prevalence of PVH in the left hemisphere, while controlling for age and sex, yields parallel results ($P=.019$, including cases with infarcts) and approaches statistical significance if cases with infarcts are excluded ($P=.066$).

Table 1.—Prevalence of Focal Neurologic Findings Among 43 Subjects With Recent Neurologic Examinations

Findings	% of Subjects
Dysarthria	5
Dysphasia	21
Dyspraxia	21
Hemianopsia	
Right	2
Left	0
Facial power	
Right	7
Left	5
Spastic tone	
Right	5
Left	5
Reflex abnormalities	
Right	37
Left	28
Right-left confusion	5
Primitive reflexes	
Glabellar	28
Suck	14
Snout	33
Rooting	5
Palmomental	
Right	40
Left	37
Limb weakness	
Right	7
Left	10
Cerebellar dysfunction	5
Abnormal gait	26
Sensory abnormality	26
Extinction	
Right	0
Left	0
Finger agnosia	5
Pollicomental	
Right	30
Left	28
Grasp	
Right	9
Left	9
Labioauricular	
Right	0
Left	0
Extensor plantar response	
Right	2
Left	2

Leuko-araiosis in the right hemisphere occurred in 27 (93%) of 29 patients with AD, in seven of eight patients with mixed dementia, and in all four patients with MID, as well as in 48 (96%) of the 50 control subjects. Leuko-araiosis could not be read on two scans. If subjects with cerebral infarcts were excluded, the prevalences in the AD and control groups changed little—to 92% and 96%, respectively. The severity of L-A does not correlate significantly with specific diagnoses; the data shown in Table 2 include subjects with radiologic infarcts. Exclusion of these subjects produces no significant change (data not shown).

Deep white-matter changes in the right hemisphere characterized 21 (72%) of the 29 patients with AD, six of eight patients with mixed dementia, and three of four patients with MID, as well as 28 (56%) of the 50 control subjects. If subjects with infarcts were excluded, the prevalence declined to 69% in the AD group and to 53% among the controls. No significant difference emerges between groups.

Subcortical L-A in the right hemisphere appeared in 25 (86%) of 29 patients with AD, in six of eight patients with mixed dementia, and in all four patients with MID, as well as in 47 (94%) of the 50 control subjects. Exclusion of subjects with infarcts yielded a prevalence of 85% in the AD group and of 93% in control subjects. The prevalence of subcortical L-A did not differ notably by diagnosis.

The presence of PVH in one hemisphere bears no link, neither in control subjects nor in patients with AD, to the presence of L-A as a whole or to the presence of subcortical L-A in the same hemisphere. Among control subjects, however, deep white-matter changes are associated with PVH (Table 3). A similar trend exists ($P = .194$) among patients with AD (Table 4). (Both Tables 3 and 4 refer to data from the right hemisphere.)

Control subjects with PVH display greater lateral ventricular dilatation (1.79 ± .99 [n = 14]) than do those without PVH (1.03 ± .69 [n = 31]) ($P = .005$). Patients with AD exhibit relatively more such dilatation than do controls, and patients with AD with PVH exhibit no more dilatation (1.93 ± .88 [n = 15]) than do those AD patients without PVH (2.00 ± .71 [n = 10]). These values represent lateral ventricular dilatation scores from the right hemisphere derived from subjects without cerebral infarcts and resemble scores from the left side. The mean sulcus widening score did not differ significantly between the cohorts with or without PVH, either in control subjects or in patients with AD.

Table 2.—Distribution of Leuko-araiosis (L-A) Scores by Diagnosis*

LA Score	AD	Control	Mixed Dementia	MID
0	2 (7)	2 (4)	1 (13)	0 (0)
1	3 (10)	10 (20)	1 (13)	0 (0)
2	5 (17)	12 (24)	0 (0)	1 (25)
3	8 (28)	15 (31)	0 (0)	1 (25)
4	11 (38)	11 (22)	6 (75)	2 (50)
Total	**29 (100)**	**50 (100)**	**8 (100)**	**4 (100)**

*AD indicates Alzheimer's disease; MID, multi-infarct dementia. Values are number (percent).

Table 3.—Prevalence of Deep White-Matter Changes and Periventricular Hyperintensity (PVH) Among Control Subjects Without Infarcts Seen on MRI Scans*

	Deep White-Matter Changes		
PVH	**Absent**	**Present**	**Totals**
Absent	19 (42)	12 (27)	**31 (69)**
Present	2 (4)	12 (27)	**14 (31)**
Totals ($P = .003$)	**21 (46)**	**24 (54)**	**45 (100)**

*MRI indicates magnetic resonance imaging. Values are number (percent).

Table 4.—Prevalence of Deep White-Matter Changes and Periventricular Hyperintensity (PVH) Among Patients With AD Without Infarcts Seen on MRI Scans*

	Deep White-Matter Changes		
PVH	**Absent**	**Present**	**Totals**
Absent	5 (20)	5 (20)	**10 (40)**
Present	3 (12)	12 (48)	**15 (60)**
Totals ($P = .194$)	**8 (32)**	**17 (68)**	**25 (100)**

*MRI indicates magnetic resonance imaging; AD, Alzheimer's disease. Values are number (percent).

Table 5.—ESD Score by Diagnosis*

	ESD Score		
Diagnosis	**Mean**	**SD**	**No. of Subjects**
AD	173.0†	53.5	28
Mixed dementia	179.8	79.9	9
Multi-infarct dementia	213.0	17.4	4
Other	178.0	. . .	1
Normal control	245.0	5.6	39

*ESD indicates Extended Scale for Dementia; AD, Alzheimer's disease.

†The mean ESD scores of the AD and control groups differ significantly ($P < .001$) (t test).

Neither in the control group nor in the AD group was there a link between L-A or either of its subcategories (deep and subcortical) and either of the two measures of atrophy (lateral ventricular dilatation and sulcus widening score).

Eighty-one subjects had ESD determinations within 6 months of MRI scanning (41 men and 40 women; mean [SD] age, 72.6 [6.9] years). They included 39 control subjects (20 men and 19 women; mean [SD] age, 73.2 [5.8] years) and 28 patients with AD (11 men and 17 women; mean [SD] age, 72.7 [7.0] years). The mean ESD scores for the diagnostic groups appear in Table 5. Subjects with infarcts seen on MRI scans were included. The mean values for the AD and control groups differed significantly, as expected. Exclusion of the three control subjects and two patients with AD with infarcts seen on MRI scans did not alter the results (data not shown).

Comparisons of the effect of the presence of PVH and of L-A—whether deep, subcortical, or both—on the mean ESD score failed to show any correlation within the AD or control groups. However, there existed a trend ($P = .097$, right hemisphere; $P = .176$, left hemisphere) for the ESD score to be lower among subjects with PVH than among those without it if control subjects and patients with AD were analyzed together. No link was found between any of the focal neurologic findings assessed and PVH, L-A, or either subcategory of L-A. This last analysis is based on a cohort of 17 men and 26 women, with a mean (SD) age of 67.5 (11.1) years.

COMMENT

Prevalence of White-Matter Changes

White-matter changes appear in 59% to 74%[18,19,44] of healthy aged subjects and in 80% of healthy middle-aged volunteers.[20] The prevalence of PVH on MRI scans likewise varies greatly. Bowen et al[12] identified PVH in 89% of 36 healthy subjects with a mean age of 70 years. Kertesz et al[8] found PVH "rims" in 98% of their 58 control subjects older than 50 years. Zimmerman et al[10] found PVH in 90% of studies with otherwise normal findings involving 63 subjects older than 30 years. The prevalence of PVH increases with age, but we find PVH in only 30% of our relatively old controls (mean age, 70 years). This may mean that changes that we denote as "deep" L-A are identified as PVH by other investigators. Also, we do not designate as PVH small triangular hyperintensities at the tips of the lateral ventricles, as other investigators may have done.

The prevalence of clinically silent changes in the white matter distant from the ventricles was reported to increase sixfold with age in one report[12] and fourfold in another report,[40] during a span of approximately 30 years; other investigators[6,29,39] have reported a similar trend. We found L-A in a similarly high percentage (96%) of control subjects. The higher prevalence of L-A and lower prevalence of PVH in our subjects compared with those of Bowen et al[12] suggests that they classify as PVH some changes that we consider to be L-A.

White-Matter Changes and Cognitive Function

Leuko-araiosis, as seen on CT scans, appears in 30%[14] to 33%[15] of patients with AD and in 10%[15] to 16%[14] of similarly aged control subjects. Other investigators[16] concur, finding relatively extensive lucencies in patients with AD. Kobari et al[43] observed L-A in 22% of young control subjects and in 62% of patients with AD, which is in agreement with findings of pathologic examination.[54] In contrast, Fazekas et al[33] found white-matter changes in 16% of controls and 13% of patients with AD. The presence of L-A correlates with decreased cognition[21] and may relate to psychomotor retardation[55] in healthy persons. Cognitive decline accompanies L-A in early AD.[22] Other studies[14,56,57] do not confirm this last observation, but our previous findings[58] support it strongly.

A weak relationship at best exists between the severity of dementia in AD and white-matter T_1[25] and T_2[26] values on MRI. Other investigators[30] have observed no association between T_1 values and cognitive decline in AD. Karlik et al[59] have suggested, based on only a few patients, that there is prolongation of T_1 in hippocampal white matter in AD.

Our findings regarding PVH establish the firmest link to date between AD and any type of change in white matter on MRI, although our neuropsychologic testing was not especially extensive. We found PVH twice as often in patients with AD compared with similarly aged control subjects (64% vs 30%), supporting the suggestion of Fazekas et al,[5] based on a smaller study, that PVH may accompany AD. Bowen et al[12] did not observe a difference in the prevalence of PVH between patients with AD and control subjects, although PVH was more widespread in the former group. Leys et al,[17] in a study based on few subjects, found a trend in this direction.

Information regarding L-A is less clear. It appears equally frequently in patients with AD and in control subjects (93% vs 96%) in our study group, as suggested by other authors.[5,6,17] Kobari et al[23] noted a tendency for L-A to appear more often, and to a greater degree, in patients with AD than in control subjects. Bowen et al[12] found a trend toward a higher prevalence of L-A in patients with AD compared with age-matched controls and a significantly greater severity of L-A in the former group. Their AD group included subjects with isolated memory disorders who did not meet criteria for dementia. These subjects displayed degrees of L-A and PVH comparable with those seen in AD. The increased involvement by PVH and L-A in that report may not, therefore, be specific for AD.

Other investigators[18,19] have stated that both L-A and mental decline in healthy aged subjects relate only to age rather than to one another. Rao et al,[20] in a study involving middle-aged subjects, reached similar conclusions. They stated the number and size range of L-A change in each subject, not an overall degree of white-matter involvement. Junque et al[39] found that L-A in subjects who are prone to cerebrovascular disease correlates with slowing of complex mental processing.

Leys et al,[17] in a study involving few subjects, reported no effect of PVH or L-A on mental function in AD. Cognitive impairment, as measured by the ESD, tends to correlate with the presence of PVH when patients with AD and control subjects are considered together, although not, as also noted by Bowen et al,[12] if the two groups are considered separately. The connection between PVH or L-A and mental impairment may bear further scrutiny, using either larger cohorts or using subjects with MID, who have more diffuse L-A.

MID

White-matter lucencies reportedly appear on CT scans in 52% to 97%[43,56,57] of patients with MID. These reports do not clearly differentiate L-A from PVH. The prevalence of L-A, based on our interpretation of the data, is between 20% and 30%.[56,57]

Small studies involving MRI[5,29] suggest that both PVH and L-A are especially extensive in MID. White-matter changes appear on MRI scans in eight of 11[40] and in all of 29[13] patients with MID, much more often than in AD[13] or in healthy subjects.[40] Periventricular hyperintensity most frequently occurs among controls but is most extensive in MID.[23] Other authors[12] have reported PVH universally in MID and AD alike, with greater severity in MID. Leuko-araiosis manifests in nine of 14[23] and in all of 12[12] patients with MID. It appears in four of nine[23] and in roughly two thirds of 87[12] patients with AD. The MID group exhibits more advanced changes.

Further investigations have assessed whether white-matter changes produce vascular dementia. Hershey et al[37] found PVH in 88% of patients with MID, a prevalence close to that seen in cognitively "borderline" (63%) and mentally intact (61%) stroke patients. Their patients with MID exhibited L-A four times as often (25% vs 6%) as did the mentally intact stroke subjects, but this finding was not statistically significant. A study of patients with lacunar infarction[48] revealed markedly more white-matter changes in demented subjects compared with "borderline" and cognitively unimpaired subjects. It remained unclear whether dementia related to L-A specifically or to lacunar infarction.

Loeb et al,[60] in contrast, found L-A more frequently among nondemented subjects with multiple strokes compared with patients with MID but did not examine its extent. Bowen et al[12] observed PVH and L-A alike in all subjects with memory complaints and Ischemic Scores in the MID range. Both changes were markedly more severe in this group than in other cohorts. Their presence did not influence the Mini-Mental Status Score.

To summarize the above, we found PVH in 75% of our patients with MID, in 38% of our patients with mixed dementia, and in 64% of our patients with AD. It occurred surprisingly infrequently in the mixed dementia group. The rather low prevalence in our MID and AD groups reflects our stringent criteria for PVH. The prevalence of L-A hovered near 90% in all of our diagnostic categories. Its severity did not differ significantly among the various groups. We found L-A in AD more often than in the roughly two thirds[12] or four tenths[17,23] of cases reported elsewhere. The low prevalence may stem from the exclusion of subjects with vascular risk factors.[17] In another instance, the authors[12] may, in comparison with our data, have underestimated L-A to the benefit of PVH.

We found, as did Bowen et al,[12] an association between L-A and MID. A demonstration that L-A contributes to intellectual decline in MID must await a large series of patients, with allowance made for the effect of stroke.

Focal Neurologic Signs and MRI White-Matter Changes

In the present report, we examined the relationship between focal signs on neurologic examination and MRI white-matter changes. Other such work, with two exceptions,[18,39] has focused on CT findings.

In a case-control study, Masdeu et al[61] identified an association between the severity of white-matter hypodensity and a history of falls. Rezek et al[16] observed a trend for motor abnormalities (abnormal tone, gait, or reflexes) to occur more frequently (67%) in patients with AD with L-A than in those without L-A (11%). No such relationship emerged among healthy control subjects. George et al[14] found gait disturbances substantially more often (45%) among demented subjects with L-A than among those without L-A (20%). Gait impairment was rare among elderly healthy subjects, regardless of the presence of L-A. George et al did not screen for other neurologic abnormalities. Steingart et al[21,22] observed, among both nondemented and demented subjects, that limb weakness and abnormal plantar responses correlated significantly with L-A. In healthy subjects,[21] gait difficulty and the rooting and palmomental reflexes also were related to L-A.

Previous studies have linked L-A, as seen on MRI scans, with gait impairment[18] and with primitive reflexes.[39] Both groups of investigators[18,39] screened only for certain focal neurologic signs. In one report,[18] the subjects were neurologically intact, which may explain why other correlations did not emerge. In the other study,[39] the presence of diverse cerebral insults may have masked an effect of L-A on focal deficits.

In patients with AD and in control subjects alike, we found that neither PVH nor L-A bears any relationship to focal neurologic signs. The absence of a correlation between L-A and either cognitive decline or focal findings supports the view[24] that L-A is a normal change in the aging brain. It clearly can reflect infarction,[27,28,42,46] however.

Periventricular hyperintensity is associated with AD and, in control subjects, with cerebral atrophy. A decrease in brain tissue may leave more free water to be resorbed at the ventricular border, yielding an increase in PVH.[10] Alternatively, PVH may result from increased transependymal seepage of ventricular fluid as a result of decreased brain hydrostatic pressure secondary to atrophy. No pathologic change, except increased water content, accompanies PVH,[34,36,47] although some investigators[24,25] dispute this.

Periventricular hyperintensity in AD does not correlate with atrophy. Patients with AD exhibit more lateral ventricular dilatation than do normal subjects with PVH. Its degree does not vary with the presence of PVH. As PVH is more common in AD than in normal subjects (64% vs 30%), its presence favors the former diagnosis. Among subjects without PVH, the presence of atrophy should suggest AD, although there is considerable overlap in the degree of atrophy exhibited by healthy subjects and patients with AD. Thus, either the presence of PVH or of atrophy without PVH may help to identify AD, while the absence of both entities may indicate normality.

In control subjects, PVH accompanies deep white-matter changes; a similar trend exists among patients with AD. The association of the two entities may reflect either a common pathogenesis, as they differ little in location, or difficulty in distinguishing between the two. Among control subjects, deep white-matter changes appear in the absence of PVH considerably more often than the converse (27% vs 4%; Table 3). This implies that deep white-matter changes herald the development of PVH in control subjects. Among patients with AD, similarly, deep white-matter changes without PVH appear slightly more often than does PVH without deep changes (20% vs 12%; Table 4). This may be explained in two ways: PVH and deep white-matter changes coexist, but neither produces the other; alternatively, the development of the latter may precede the appearance of the former, with this effect submerged in AD by a high prevalence of PVH from another cause.

The genesis of PVH in AD is unclear. White-matter changes seen on CT scans have been related to the presence of hypertension and of infarcts seen on CT scans[15] in a population of demented subjects. Rezek et al[16] found significantly elevated systolic blood pressures among patients with AD who exhibited white-matter changes compared with other patients with AD; some investigators[62] have observed the opposite trend. The absence of marked arteriolar changes in the white matter of some,[16,54,63] though not all,[14] patients with AD who exhibit white-matter lucencies has focused attention on other factors: cerebral amyloid angiopathy[38,64] and even hypotension.[54] The former involves meningeal vessels remote from the ventricle and likely produces L-A, not PVH. Increased water content or tissue loss in the white matter may generate PVH via the mechanisms postulated earlier. Increased water content appears in the white matter of patients with AD on autopsy.[54,63] One group[25,31] reported an increased T_1 value in the white matter of patients with AD relative to controls, but another group[30] did not. The presence or absence of PVH may help to diagnose or exclude AD, even though the cause of PVH itself remains uncertain.

Leuko-araiosis, as identified by MRI, embraces common and subtle changes of unclear cause. On microscopic examination,[24,27,28,42,45-47] some L-A represents areas of infarction, gliosis, or demyelination. It may also reflect other entities (etat crible, cysts, ventricular diverticulae, or venous angiomas) that spare the brain parenchyma and should not compromise neurologic function.

Although severe L-A can produce dementia,[65] its heterogeneity and often limited extent render assessment of its effects difficult. Prospective investigation involving more subjects and detailed neuropsychologic, neuroradiologic, and neurologic evaluations will resolve the issue. The effect of L-A may be more evident when it is more severe, as in MID; with MID, however, one must contend with the confounding effects of stroke. Leuko-araiosis may constitute a risk factor or marker for the development of mental decline, even if it produces no incapacity itself. Appropriate observation over time will yield the answer. Lastly, proper ascertainment of coexisting conditions will identify the causes of L-A and guide future treatment.

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References

1. Bradley WG, Waluch V, Brant-Zawadzki M, Yadley RA, Wycoff RR. Patchy periventricular white matter lesions in the elderly: a common observation during NMR imaging. *Noninvasive Med Imaging*. 1984;1:35-42.
2. Salgado ED, Weinstein M, Furlan AJ, et al. Proton magnetic resonance imaging in ischemic cerebrovascular diseases. *Ann Neurol*. 1986;20:502-507.
3. Young IR, Randell CP, Kaplan PW, James A, Bydder GM, Steiner RE. Nuclear magnetic resonance (NMR) imaging in white matter disease of the brain using spin-echo sequences. *J Comput Assist Tomogr.* 1983;7:290-294.
4. Awad IA, Spetzler RF, Hodak JA, Awad CA, Carey R. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, I: correlation with age and cerebrovascular risk factors. *Stroke*. 1986;17:1084-1089.
5. Fazekas F, Chawluk JB, Alavi A, Hurtig HI, Zimmerman RA. MR signal abnormalities at 1.5T in Alzheimer's dementia and normal aging. *Am J Neuroradiol*. 1987;8:421-426.
6. George AE, de Leon MJ, Kalnin A, Rosner L, Goodgold A, Chase N. Leukoencephalopathy in normal and pathologic aging, II: MRI of brain lucencies. *Am J Neuroradiol*. 1986;7:567-570.
7. Gerard G, Weisberg LA. MRI periventricular

lesions in adults. *Neurology.* 1986;36:998-1001.

8. Kertesz A, Black SE, Tokar G, Benke T, Carr T, Nicholson L. Periventricular and subcortical hyperintensities on MRI: 'rims, caps and unidentified bright objects.' *Arch Neurol.* 1988;45:404-408.

9. Sarpel G, Chaudry F, Hindo W. Magnetic resonance imaging of periventricular hyperintensity in a Veterans Administration hospital population. *Arch Neurol.* 1987;44:725-728.

10. Zimmerman RD, Fleming CA, Lee BCP, Saint-Louis LA, Deck MDF. Periventricular hyperintensity as seen by magnetic resonance: prevalence and significance. *Am J Neuroradiol.* 1986;7:13-20.

11. Hachinski VC, Potter P, Merskey H. Leukoaraiosis: an ancient term for a new problem. *Arch Neurol.* 1987;44:21-23.

12. Bowen BC, Barker WW, Loewenstein DA, Sheldon J, Duara R. MR signal abnormalities in memory disorder and dementia. *Am J Neuroradiol.* 1990;11:283-290.

13. Erkinjuntti T, Ketonen L, Sulkava R, Sipponen J, Vuorialho M, Iivanainen M. Do white matter changes on MRI and CT differentiate vascular dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry.* 1987;50:37-42.

14. George AE, de Leon MJ, Gentes CI, et al. Leukoencephalopathy in normal and pathologic aging, I: CT of brain lucencies. *Am J Neuroradiol.* 1986;7:561-566.

15. Inzitari D, Diaz F, Fox A, et al. Vascular risk factors and leuko-araiosis. *Arch Neurol.* 1987;44:42-47.

16. Rezek DL, Morris JC, Fulling KH, Gado MH. Periventricular white matter lucencies in senile dementia of the Alzheimer type and in normal aging. *Neurology.* 1987;37:1365-1368.

17. Leys D, Soetaert G, Petit H, Fauquette A, Pruvo JP, Steinling M. Periventricular and white matter magnetic resonance imaging hyperintensities do not differ between Alzheimer's disease and normal aging. *Arch Neurol.* 1990;47:524-527.

18. Hendrie HC, Farlow MR, Austrom MG, Edward MK, Williams MA. Foci of increased T2 signal intensity on brain MR scans of healthy elderly subjects. *Am J Neuroradiol.* 1989;10:703-707.

19. Hunt AL, Orrison WW, Yeo RA, et al. Clinical significance of MRI white matter lesions in the elderly. *Neurology.* 1989;39:1470-1474.

20. Rao SM, Mittenberg W, Bernardin L, Haughton V, Leo GJ. Neuropsychological test findings in subjects with leukoaraiosis. *Arch Neurol.* 1989;46:40-44.

21. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in subjects with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). *Arch Neurol.* 1987;44:32-35.

22. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in demented patients with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). *Arch Neurol.* 1987;44:36-39.

23. Kobari M, Meyer JS, Ichijo M, Oravez WT. Leukoaraiosis: correlation of MR and CT findings with blood flow, atrophy, and cognition. *Am J Neuroradiol.* 1990;11:273-281.

24. Awad IA, Johnson PC, Spetzler RF, Hodak JA. Incidental subcortical lesions identified on magnetic resonance imaging in the elderly, II: postmortem pathological correlations. *Stroke.* 1986;17:1090-1097.

25. Besson JAO, Corrigan FM, Iljon Foreman E, Eastwood LM, Smith FW, Ashcroft GW. Nuclear magnetic resonance (NMR), II: imaging in dementia. *Br J Psychiatry.* 1985;146:31-35.

26. Bondareff W, Raval J, Colletti PM, Hauser DL. Quantitative magnetic resonance imaging and the severity of dementia in Alzheimer's disease. *Am J Psychiatry.* 1988;145:853-856.

27. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology, I: lacunar infarction and Virchow-Robin spaces. *Am J Neuroradiol.* 1988;9:621-628.

28. Braffman BH, Zimmerman RA, Trojanowski JQ, Gonatas NK, Hickey WF, Schlaepfer WW. Brain MR: pathologic correlation with gross and histopathology, II: hyperintense white-matter foci in the elderly. *Am J Neuroradiol.* 1988;9:629-636.

29. Brant-Zawadzki M, Fein G, Van Dyke C, Kiernan R, Davenport L, deGroot J. MR imaging of the aging brain: patchy white-matter lesions and dementia. *Am J Neuroradiol.* 1985;6:675-682.

30. Christie JE, Kean DM, Douglas RHB, Engleman HM, St Clair D, Blackburn IM. Magnetic resonance imaging in pre-senile dementia of the Alzheimer type, multi-infarct dementia and Korsakoff's syndrome. *Psychol Med.* 1988;18:319-329.

31. Ebmeier KP, Besson JAO, Crawford JR, et al. Nuclear magnetic resonance imaging and single photon emission tomography with radio-iodine labelled compounds in the diagnosis of dementia. *Acta Psychiatr Scand.* 1987;75:549-556.

32. Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke.* 1988;19:1285-1288.

33. Fazekas F, Alavi A, Chawluk JB, et al. Comparison of CT, MR, and PET in Alzheimer's dementia and normal aging. *J Nucl Med.* 1989;30:1607-1615.

34. Gado MH, Torack R, Morris J. Periventricular high signal (PVHS) and correlation with histologic examination: a post-mortem study. Presented at the 26th Meeting of the American Society of Neuroradiology; May 15-20, 1988; Chicago, Ill.

35. Heier LA, Bauer CJ, Schwartz L, Zimmerman RD, Morgello S, Deck MDF. Large Virchow-Robin spaces: MR-clinical correlation. *Am J Neuroradiol.* 1989;10:929-936.

36. Heier LA, Morgello S, Farrar JT, Zimmerman RD, Deck MDF. Periventricular hyperintensities: MR-pathologic correlations between subcortical and subependymal hyperintensities. Presented at the 26th Meeting of the American Society of Neuroradiology; May 15-20, 1988; Chicago, Ill.

37. Hershey LA, Modic MT, Greenough PG, Jaffe DF. Magnetic resonance imaging in vascular dementia. *Neurology.* 1987;37:29-36.

38. Janota I, Mirsen TR, Hachinski VC, Lee DH, Merskey H. Neuropathologic correlates of leuko-araiosis. *Arch Neurol.* 1989;46:1124-1128.

39. Junque C, Pujol J, Vendrell P, et al. Leukoaraiosis on magnetic resonance imaging and speed of mental processing. *Arch Neurol.* 1990;47:151-156.

40. Kertesz A, Polk M, Carr T. Cognition and white matter changes on magnetic resonance imaging in dementia. *Arch Neurol.* 1990;47:387-391.

41. Kinkel WR, Jacobs R, Polachini I, Bates V, Heffner RR Jr. Subcortical arteriosclerotic encephalopathy (Binswanger's disease): computed tomographic, nuclear magnetic resonance, and clinical correlations. *Arch Neurol.* 1985;42:951-959.

42. Kirkpatrick JB, Hayman LA. White matter lesions in MR imaging of clinically healthy brains of elderly subjects: possible pathologic basis. *Radiology.* 1987;162:509-511.

43. Kobari M, Meyer JS, Ichijo M. Leuko-araiosis, cerebral atrophy, and cerebral perfusion in normal aging. *Arch Neurol.* 1990;47:161-165.

44. Lechner H, Schmidt R, Bertha G, Justich E, Offenbacher H, Schneider G. Nuclear magnetic resonance image white matter lesions and risk factors for stroke in normal individuals. *Stroke.* 1988;19:263-265.

45. Leifer D, Buonanno FS, Richardson EP Jr. Clinicopathologic correlations of cranial magnetic resonance imaging of periventricular white matter. *Neurology.* 1990;40:911-918.

46. Marshall VG, Bradley WG, Marshall CE, Bhoopat T, Rhodes RH. Deep white matter infarction: correlation of MR imaging and histopathologic findings. *Radiology.* 1988;167:517-522.

47. Sze G, De Armond SJ, Brant-Zawadzki M, Davis RL, Norman D, Newton TH. Foci of MRI signal (pseudolesions) anterior to the frontal horns: histologic correlations of a normal finding. *Am J Neuroradiol.* 1986;7:381-387.

48. Tanaka Y, Tanaka O, Mizuno Y, et al. A radiologic study of dynamic processes in lacunar dementia. *Stroke.* 1989;20:1488-1493.

49. Hersch EL. Development and application of the extended scale for dementia. *J Am Geriatr Soc.* 1979;27:348-354.

50. Lau C, Wands K, Merskey H, et al. Sensitivity and specificity of the extended scale for dementia. *Arch Neurol.* 1988;45:849-852.

51. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition.* Washington, DC: American Psychiatric Association; 1980:107-112.

52. Hachinski VC, Iliff LD, Zilkha E, et al. Cerebral blood flow in dementia. *Arch Neurol.* 1975;32:632-637.

53. Wade JPH, Mirsen TR, Hachinski VC, Fisman M, Lau C, Merskey H. The clinical diagnosis of Alzheimer's disease. *Arch Neurol.* 1987;44:24-29.

54. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer type: a pathoanatomical study. *Ann Neurol.* 1986;19:253-262.

55. Kluger A, Gianutsos J, de Leon MJ, George AE. Significance of age-related white matter lesions. *Stroke.* 1988;19:1054-1055. Letter.

56. Aharon-Peretz J, Cummings JL, Hill MA. Vascular dementia and dementia of the Alzheimer type: cognition, ventricular size, and leuko-araiosis. *Arch Neurol.* 1988;45:719-721.

57. Erkinjuntti T, Sulkava R, Palo J, Ketonen L. White matter low attenuation on CT in Alzheimer's disease. *Arch Gerontol Geriatr.* 1989;8:95-104.

58. Diaz JF, Merskey H, Hachinski VC, et al. Improved recognition of leukoaraiosis and cognitive impairment in Alzheimer's disease. *Arch Neurol.* 1991;48:000-000.

59. Karlik SJ, Fox AJ, Lee DH. MRI in dementia. Presented at the 14th Meeting of the Symposium Neuroradiologicum; June 17-23, 1990; London, England.

60. Loeb C, Gandolfo C, Bino G. Intellectual impairment and cerebral lesions in multiple cerebral infarcts: a clinical-computed tomography study. *Stroke.* 1988;19:560-565.

61. Masdeu JC, Wolfson L, Lantos G, et al. Brain white-matter changes in the elderly prone to falling. *Arch Neurol.* 1989;46:1292-1296.

62. Erkinjuntti T, Ketonen L, Sulkava R, Vuorialho M, Palo J. CT in the differential diagnosis between Alzheimer's disease and vascular dementia. *Acta Neurol Scand.* 1987;75:262-270.

63. Besson JAO, Ebmeier KP, Best PV, Smith FW. Do white matter changes on MRI and CT differentiate vascular dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry.* 1988;51:318-319.

64. Gray F, Dubas F, Roullet E, Escourolle R. Leukoencephalopathy in diffuse hemorrhagic cerebral amyloid angiopathy. *Ann Neurol.* 1985;18:54-59.

65. Janota I. Dementia, deep white matter damage and hypertension: 'Binswanger's disease.' *Psychol Med.* 1981;11:39-48.

Improved Recognition of Leukoaraiosis and Cognitive Impairment in Alzheimer's Disease

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• We identified 85 patients in a longitudinal study of dementia who had uncomplicated Alzheimer's disease and in whom computed tomography of the head and psychometric testing were conducted within a 6-month period following their entry into the study. Thirty-four patients (40%) had leukoaraiosis, which was disproportionately common in female patients (62% vs 15% in male patients). Analysis of covariance demonstrated a relative reduction of scores on the Extended Scale for Dementia in those patients who had leukoaraiosis, after adjusting for the confounding effects of age, sex, educational level, and duration of illness. Leukoaraiosis was also much more common in women, even after adjusting for the possible confounding effects of age, duration of illness, Extended Scale for Dementia score, and hypertension. Multiple regression analysis showed that leukoaraiosis accounted for 11.6% of the variance of the Extended Scale for Dementia scores. Leukoaraiosis, together with duration of illness, accounted for 18.2% of the variance. Leukoaraiosis is associated with a greater degree of cognitive impairment in patients with Alzheimer's disease.

(*Arch Neurol.* 1991;48:1022-1025)

Hypodensities of white matter on computed tomographic (CT) scans, described as leukoaraiosis (LA),[1] are more frequently associated with Alzheimer's disease (AD) than with normal aging.[2-6] However, the relationship between LA and the degree of cognitive impairment in subjects with AD remains unsettled. Contradictory results from previous studies[2,5,7,8] may be due to differences in the populations sampled, the criteria for both AD and LA, or the sensitivity of various psychometric tests of intellectual impairment. The sensitivity of the scanner and the experience of the radiologist may also be relevant.

Furthermore, the relationship between LA and cognitive impairment may be confounded by a number of variables. Age,[4,5,9-11] stroke, hypertension,[10,12-17] and severity of AD[4,5,7] are all related to LA. Perhaps duration of illness could also affect the occurrence of LA. Cognitive ability decreases with age,[18] stroke,[19] hypertension,[20] and the duration and severity of AD. Formal education may confound the relationship because it influences psychometric test performance.[18] However, these effects may not fully explain the association between LA and intellectual impairment.[4,5]

In the present study, we compared patients with AD with LA and without LA in terms of the degree of cognitive impairment, taking into consideration potential confounding effects of other variables.

PATIENTS AND METHODS

The patients were selected from the University of Western Ontario (London) Dementia Study, a longitudinal research project described elsewhere.[21,22] They included all the patients clinically diagnosed as having AD according to the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised*, criteria[23] who had undergone CT scanning of the head and psychometric testing completed within a 6-month period following their entry into the study. A history of stroke, cerebral infarcts as seen on CT scans, and a primary neuropathologic diagnosis other than AD made post mortem were used as exclusion criteria to maximize the diagnostic accuracy of AD. Forty-five patients had died, and the diagnosis of AD was confirmed in 25 patients during autopsy. In the other 20 patients, postmortem examination was not performed.

The study sample included 59 patients from the group of patients discussed in a previous study[5] who satisfied the above criteria as well as an additional 26 new cases. Our study differed from the previous one[5] in that all CT scans were newly interpreted, and additional variables were analyzed.

The clinical diagnosis was established by a research fellow in neurology (T.R.M. or J.F.D.) and reviewed by one of us (V.C.H.). It was based on a systematic comprehensive evaluation.[21,22] When compared with the postmortem neuropathologic diagnosis in a subsample of patients, the clinical diagnosis of AD showed an overall accuracy of 83.1%, a sensitivity of 86.8%, and a specificity of 77.8%.[22]

CT Study

Two different CT scanners were used. Subjects who entered the study before October 1986 underwent scanning with a GE 8800 model scanner (General Electric, Milwaukee, Wis); the remainder underwent scanning with an updated GE 9800 model (General Electric). Both scanners were set for a 10-mm section thickness; 5-mm contiguous sections were obtained through the temporal lobes. No contrast material was used.

Compared with the GE 8800 scanner, the GE 9800 model reduces beam-hardening ar-

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tifact and shortens the scanning time (2.4 seconds vs 2.8 seconds), which reduces the effects of patient motion and improves resolution (0.35 to 0.45 mm vs 0.75 mm). The new scanner also features an increase in the scanning aperture and in the amount of maximum gantry tilt. As a result, lesions were better visualized with the updated GE 9800 scanner.

A neuroradiologist (D.H.L.) interpreted all the CT scans in a "blinded" manner. The presence of LA and infarcts was established on the basis of specific criteria.[24] Moderate to substantial interobserver agreement has been shown in a subsample of CT scans, as reflected by mean pairwise κ values of .67 for LA and .57 for infarcts.[4]

Leukoaraiosis was categorized as focal when two or fewer areas of ill-defined hypodensity were seen in a hemisphere and as diffuse when more than two areas of hypodensity or confluent hypodensity were seen in a hemisphere.

Psychometric Testing

Cognitive impairment was graded by the Extended Scale for Dementia (ESD),[25] which was developed as a revision of the Mattis Dementia Scale.[26] The total ESD score is derived from 23 weighted subscores and has a maximum of 250 points. The lower the score, the more profound the cognitive impairment. Two psychometrists completed all the ESD measurements without knowledge of the CT findings.

The ESD demonstrates mild to severe degrees of cognitive decline with high test-retest reliability ($r=.94$) and internal consistency (Kuder-Richardson 20 coefficient of .943).[25] With a cutoff point of 221, the ESD discriminated demented from nondemented elderly subjects with an overall accuracy of 94%.[27]

Variables

The sociodemographic characteristics under study included age, sex, the highest level of formal education attained, and occupation. Social class was graded on a scale for Canadian occupations.[28] The other variables included the duration of dementia (as elicited from the next of kin), the ischemia score,[29] the electroencephalographic grade of abnormality,[30] hypertension, blood pressure values, and ESD score. On the CT scan, the presence or absence of LA and its type (diffuse or focal) were noted.

Hypertension was defined as the presence of one or more of the following: (1) a systolic blood pressure greater than 160 mm Hg, (2) a diastolic blood pressure greater than 90 mm Hg, and (3) a previous medical diagnosis of hypertension. The blood pressure values were recorded from the right arm while the subject was seated.

Statistical Analyses

Univariate analyses, with use of the χ^2 test for dichotomous or categorical variables and the Pearson correlation coefficients and two-tailed t-tests for continuous variables, were performed to assess the relationships among the study variables. Analysis of covariance and multiple regression analysis were used to explore the association between LA and ESD scores while simultaneously controlling for confounding effects from other variables. Multiple logistic regression was used to examine the effect of sex on LA while adjusting for other potential confounders. The analyses were performed with the SPSSX[31] and the SAS.[32]

RESULTS

The 85 patients had a mean (±SD) age of 70.8±8.4 years. Forty-five patients (52.9%) were female, and 83 (98%), including all of those with LA, had an ischemia score[29] of 4 or lower, which supported the diagnosis of AD. The ischemia score was missing in one patient, but AD was diagnosed during the postmortem examination. One patient without LA had an ischemia score of 5, but the course of his illness and the absence of infarcts on CT scans supported the clinical diagnosis of AD.

Leukoaraiosis was present in 34 (40%) of the patients. Diffuse LA was identified in 10 cases (12%) and focal LA in 24 (28%). Forty percent of the patients had had hypertension. The mean duration of the illness to the time of CT scanning was 4.1±2.6 years, with a median of 3.4 years. The mean duration for those with onset before the age of 65 years compared with those with onset after the age of 65 showed only a small difference that did not suggest earlier diagnosis of those still employed (onset before age 65 years, 4.7±3.14 years; onset after age 65 years, 3.91±2.25 years).

The mean ESD score was 132.1±80.8, with a range of 0 to 237. The intellectual impairment was considered mild (ESD score greater than 189) in 35.3% of the patients, moderate (ESD score, 70 to 189) in 36.5% of patients, severe (ESD score, 21 to 69) in 10.6% of patients, and advanced (ESD score, 0 to 20) in 17.6% of patients. The new scanner was used in only nine cases, identifying LA in three cases. The old scanner was used in the remaining 76 cases, showing LA in 41% (Fisher's Exact Test [two-tailed], $P=.74$). Information was lacking concerning the educational level of six patients. Only 4% of the patients for whom this information was available had not attended school. Forty percent had attended elementary school or some high school, and 56% had completed high school or attended a college or university.

Table 1.—Clinical Characteristics of the Patients With and Without Leukoaraiosis*

	Leukoaraiosis	
Variable	Absent (n = 51)	Present (n = 34)
ESD score	154.4 (75.3)†	98.6 (78.1)†
Duration of dementia, y	3.8 (2.0)	4.6 (3.3)
EEG		
Normal	15.5	13.3
Mild abnormality	37.8	20.0
Moderate abnormality	28.9	30.0
Severe abnormality	17.8	36.7
Hypertension	31.4	38.2
Systolic blood pressure, mm Hg	138.5 (20.5)	140.0 (19.7)
Diastolic blood pressure, mm Hg	78.9 (10.2)	76.7 (9.5)

*Values are mean (SD) or percent. ESD indicates Extended Scale for Dementia; EEG, electroencephalogram.

†$P < .001$.

Table 2.—Sociodemographic Variables of Patients With and Without Leukoaraiosis*

	Leukoaraiosis		
Variable	Absent (n = 51)	Present (n = 34)	P
Age, y	68.0 (8.6)	75.1 (6.0)	.0001
Sex			
M (n = 40)	85.0	15.0	.0001
F (n = 45)	37.8	62.2	
Education			
≤Grade 11 (n = 35)†	62.9	37.1	.5
Grade 12+ (n = 44)†	56.8	43.2	

*Values are mean (SD) or percent.

†Information on education was not available for six patients.

Tables 1 and 2 compare the clinical and sociodemographic characteristics of the subjects in terms of LA. Cognitive impairment was more pronounced in the group with LA compared with the group without LA. A 56-point mean difference in the ESD score was both clinically and statistically significant. However, no significant difference in the ESD score emerged between patients with diffuse and focal LA who scored 107±76.8 vs 95±80.0, respectively ($P=.7$). Except for the categories of "counting backward" and "counting by threes," all 23 mean ESD subscores were significantly lower in the group with LA ($P<.05$).

A higher degree of electroencephalographic abnormalities, reflecting more severe disease, in those patients exhibiting LA is consistent with their lower ESD score.[28] The more pronounced cognitive deterioration of the patients with LA could not be explained by longer duration of their AD. However, those with LA were significantly older ($P<.0001$) and predominantly female ($P<.0001$). No significant differences were found for education, social class, and blood pressure values. The effect of sex on LA was examined further by logistic regression analysis, including sex, age, duration of illness, hypertension, and ESD score as predictor variables for LA. The effect of sex on LA remained significant ($P<.0003$) after adjusting for the other sigificant confounding variables (age and ESD score), the odds ratio for the occurrence of LA in female patients being 9.96.

As expected, the ESD score was inversely correlated with age ($r = -.13$, $P = .22$) and duration of AD ($r = -.31$, $P = .004$). Female patients showed a significantly lower mean ESD score than did male patients (116 ± 78.8 vs 150 ± 76.5; $P = .05$). Patients with grade 11 and lower educational levels showed a lower mean ESD score (126 ± 74.2) compared with those with a higher educational level (140 ± 83.0), but the difference did not reach statistical significance. No significant associations emerged between ESD score and hypertension or blood pressure values.

In summary, the univariate analysis showed an association between LA and lower ESD scores and suggested potential confounding effects from age, sex, duration of AD, and educational level. Therefore, a multivariate analysis was performed to control for these effects.

Examination of the ESD score as a function of LA, age, sex, and duration of illness with analysis of covariance revealed significant effects from LA ($P = .01$) and duration of illness ($P = .02$) but no significant effects from age ($P = .52$) or sex ($P = .87$). A simplified model, including only LA and duration of the dementia, showed significant effects from both variables ($P = .003$ and $P = .01$, respectively).

Multiple regression analysis showed that LA alone accounted for 11.6% of the variation in ESD scores, while LA and duration together accounted for 18.2%. Adding age and sex to the model increased the explained variation of the ESD scores by only 0.37%. Therefore, among the variables introduced in the model, only LA and duration of illness were significantly associated with cognitive impairment. However, LA alone explains only approximately one tenth of the variation in cognitive impairment observed in patients with AD.

COMMENT

Our study results show that the presence of LA is associated with increased cognitive impairment in AD after taking into consideration the confounding effects of age, sex, duration of illness, and the level of formal education. However, LA accounts for only a small proportion of the variation in cognitive impairment, suggesting that other factors associated with the degenerative process of AD may account for most of the cognitive deterioration seen in AD.

An association between the severity of LA and the severity of AD was reported by George et al[2] but was not confirmed by Erkinjuntti et al.[7] Rezek et al[38] showed a relationship between the extent of LA and intellectual decline. Findings of a longitudinal study[8] showed that patients with early AD experienced the same intellectual decline, regardless of the presence or absence of LA. However, previous data from our group[5] showed that LA accompanied lower scores on the ESD only in the less advanced cases of AD. Magnetic resonance imaging studies have also yielded contradictory findings,[17,34-36] which are discussed in another report by our group (T.R.M., D.H.L., C.J.W., et al, unpublished data, 1990). Discrepant results from CT and magnetic resonance imaging studies may be due to differences in the study samples, criteria for both AD and LA, the potential of the psychometric tests to measure various degrees of intellectual impairment, and the sensitivity of the scanner to detect LA.

Previously published CT studies have reported a frequency of LA with AD ranging from 13%[37] to 19.7%[7] to 30%.[2] Our group previously reported a frequency of 33%[16] in patients, many of whom were included in the current study. The differences appear to be due to methodologic variations from other studies and to improved recognition of LA with experience. The predominance of LA in women in our study after allowing for possible confounding variables is unexplained. We previously reported increased LA in men,[16] but that study also included patients with overt vascular disease. The present report deals with a group that, to our knowledge, has only AD.

The improvements in our study are the increased accuracy in the detection of LA, the use of analyses to control for the confounding effects from other variables, and the inclusion of patients with a wide degree of impairment. As in the past,[22] we have supported the diagnosis of AD in our patients by continued clinical follow-up, neuropathologic data, and the exclusion of patients with stroke and infarcts as seen on CT scans.

The cross-sectional design of this study does not permit conclusions to be drawn regarding causality. Therefore, the present results showing a clear association between LA and the degree of intellectual decline support the need for a longitudinal study to clarify the question of whether LA contributes to the intellectual deterioration observed in AD.

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References

1. Hachinski VC, Potter P, Merskey H. Leuko-araiosis. *Arch Neurol.* 1987;44:21-23.

2. George AE, de Leon MJ, Gentes CT, et al. Leukoencephalopathy in normal and pathological aging, I: CT of brain lucencies. *Am J Neuroradiol.* 1986;7:567-570.

3. Brun A, Englund E. A white matter disorder in dementia of the Alzheimer's type: a patho-anatomical study. *Ann Neurol.* 1986;19:253-262.

4. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in subjects with diffuse white matter lucencies on computed tomographic scan (leuko-araiosis). *Arch Neurol.* 1987;44:32-35.

5. Steingart A, Hachinski VC, Lau C, et al. Cognitive and neurologic findings in demented patients with diffuse white matter lucencies on computed tomographic scan. *Arch Neurol.* 1987;44:36-39.

6. Kobari M, Meyer JS, Ichijo M. Leuko-araiosis, cerebral atrophy and cerebral perfusion in normal aging. *Arch Neurol.* 1990;47:161-165.

7. Erkinjuntti T, Sulkava R, Palo J, Ketonen L. White matter low attenuation on CT in Alzheimer's disease. *Arch Gerontol Geriatr.* 1989;8:95-104.

8. Morris JC, Goto MH, Grant EA, Rezek DL. Periventricular white matter lucencies: no effect on the natural history of senile dementia of the Alzheimer's type. *Ann Neurol.* 1988;24:158-159.

9. Valentine AR, Moseley IF, Kendall BE. White matter abnormality in cerebral atrophy: clinicopathological correlations. *J Neurol Neurosurg Psychiatry.* 1980;43:139-142.

10. Goto K, Ishii N, Fukasawa H. Diffuse white matter disease in the geriatric population. *Radiology.* 1981;141:687-695.

11. Gerard G, Weisberg LA. MRI periventricular lesions in adults. *Neurology.* 1986;36:998-1001.

12. Caplan LR, Schoene WC. Clinical features of subcortical encephalopathy (Binswanger disease). *Neurology (Minneapolis).* 1978;28:1206-1215.

13. Loizou LA, Kendall BE, Marshall J. Subcortical arteriosclerotic encephalopathy: a clinical and radiological investigation. *J Neurol Neurosurg Psychiatry.* 1981;44:294-304.

14. Kinkel WR, Jacobs L, Polachini I, Bates V, Heffner RR Jr. Subcortical arteriosclerotic encephalopathy (Binswanger's disease): computed tomographic, nuclear magnetic resonance, and clinical correlations. *Arch Neurol.* 1985;42:951-959.

15. Huang K, Wu L, Luo Y. Binswanger's disease: progressive sub-cortical encephalopaty or multi-infarct dementia? *Can J Neurol Sci.* 1985;12:88-94.

16. Inzitari D, Diaz JF, Fox A, et al. Vascular

risk factors and leuko-araiosis. *Arch Neurol.* 1987;44:42-47.

17. Erkinjuntti T, Ketonen L, Sulkava R, Sipponen I, Vuorialho M, Divanainen M. Do white matter changes on MRI and CT differentiate vascular dementia from Alzheimer's disease? *J Neurol Neurosurg Psychiatry.* 1987;50:37-42.

18. Birren JE. Research on the psychologic aspects of aging. *Geriatrics.* 1963;18:393-403.

19. Hachinski VC, Lassen NA, Marshall J. Multi-infarct dementia: a case of mental deterioration in the elderly. *Lancet.* 1974;2:207-210.

20. Wilkie F, Eisdorfer C. Intelligence and blood pressure in the aged. *Science.* 1971;172:959-962.

21. Merskey H, Blume WT, Colhoun EH, et al. Correlative studies in Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry.* 1985;9:509-514.

22. Wade JPH, Mirsen TR, Hachinski VC, et al. The clinical diagnosis of Alzheimer's disease. *Arch Neurol.* 1987;44:24-29.

23. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition Revised.* Washington, DC: American Psychiatric Association; 1987.

24. Lee D, Fox A, Vinuela F, et al. Interobserver variation in computed tomography of the brain. *Arch Neurol.* 1987;44:30-31.

25. Hersch EL. Development and application of the Extended Scale for Dementia. *J Am Geriatr Soc.* 1979;27:348-354.

26. Coblentz JM, Mattis S, Zingesser H, Kassoff SS, Wisniewski HM, Katzman R. Presenile dementia. *Arch Neurol.* 1973;29:299-309.

27. Lau C, Wands K, Merskey H, et al. Sensitivity and specificity of the Extended Scale for Dementia. *Arch Neurol.* 1988;45:849-852.

28. Blishen BR, McRoberts HA. A revised socio-economic index for occupations in Canada. *Can Rev Soc Anthropol.* 1976;13:71-73.

29. Hachinski VC, Illif LD, Zilkha E, et al. Cerebral blood flow in dementia. *Arch Neurol.* 1975;32:632-637.

30. Rae-Grant A, Blume W, Lau C, Hachinski VC, Fisman M, Merskey H. The electroencephalogram in Alzheimer-type dementia. *Arch Neurol.* 1987;44:50-54.

31. *Statistical Package for the Social Sciences.* Chicago, Ill: SPSS Inc; 1988.

32. *Statistical Analysis System, Version 6.* Cary, NC: SAS Institute Inc; 1990.

33. Rezek DL, Morris JC, Fulling KH, Gado MH. Periventricular white lucencies in senile dementia of the Alzheimer type and in normal aging. *Neurology.* 1987;37:1365-1368.

34. Clark C, Welsh K, Earl N. The association of T2 signals on magnetic resonance imaging with cognitive impairment in patients with clinical Alzheimer's disease. *Ann Neurol.* 1988;24:161.

35. Wilson RS, Bennett D, Fox JH, et al. Alzheimer's disease: prevalence ands clinical significance of white-matter lesions on magnetic resonance imaging. *Ann Neurol.* 1988;24:160-161.

36. Bowen BC, Barker WW, Loewenstein DA, Sheldon J, Duara R. MR signal abnormalities in memory disorder and dementia. *Am J Neuroradiol.* 1990;11:283-290.

37. Fazekas F, Alavi A, Chawluk JB, et al. Comparison of CT, MR, and PET in Alzheimer's dementia and normal aging. *J Nucl Med.* 1989;30:1607-1615.

Cerebrovascular Instability in a Subset of Patients With Stroke and Transient Ischemic Attack

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• In six patients, we observed remarkably unsteady blood flow and indications of vasospasms on the arteriolar level in connection with episodes of focal cerebral ischemia. The patients originated from a prospective consecutive study of 53 patients with stroke and transient ischemic attack who had been examined by cerebral angiography and rapidly repeated regional cerebral blood flow measurements using the intracarotid xenon 133 method. In 47 patients, regional cerebral blood flow values, flow patterns, and clinical condition were stable during the repeated regional cerebral blood flow measurements. In six patients, pronounced regional hypoperfusion and hyperperfusion developed during the course of examination. In the hypoperfused regions, flow was transiently reduced to values consistent with ischemia, and in four of these patients this was accompanied by transient neurological deficits. The arteriogram and isotope angiograms ruled out spasms of large arteries or thromboembolism. A condition of cerebrovascular instability on the arteriolar level probably was induced by the examination procedure. These patients were hypersensitive to the provoking stimuli either habitually or as a consequence of previous ischemic accidents. It is suggested that in some patients with focal cerebral ischemia, the primary cause might be spasms of the smallest resistance vessels rather than thromboembolism.

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A major part of focal cerebral accidents are due to thromboembolism. Arterial spasms have been considered another possible cause of focal cerebral ischemia. However, with the exception of cases of subarachnoid hemorrhage, arterial spasms have only rarely been demonstrated on cerebral angiograms. Consequently, vasospasms generally have been rejected as a possible pathophysiological mechanism of focal cerebral ischemia in patients with transient ischemic attack (TIA) and stroke. In this article, we present evidence that vasospasms in fact might be a cause of focal cerebral ischemia in some patients suffering from TIA and stroke. However, these spasms occur on the level of the smallest cerebral resistance vessels and are therefore not visible on a cerebral angiogram. We focus on the description of six patients from a consecutive study of 53 patients with recent cerebral ischemic events. During measurements of regional cerebral blood flow (rCBF), we found a remarkably unsteady regional perfusion of the cerebral cortex, suggesting instability of the cerebrovascular tone. In these six patients, we failed to demonstrate embolic sources, and there were no spasms of the vessels visible on the angiogram. In five patients, there were no angiographic signs of vascular occlusions.

PATIENTS AND METHODS

Patients

This report describes the investigation of six patients from a group of 53 who were examined consecutively in a prospective study. They were admitted to the hospital in direct connection with the appearance of neurological symptoms suggesting acute ischemic cerebral accidents. Patients with severe, disabling diseases or advanced malignant diseases were not included in the study. Excluded from this study were patients with brain-stem and cerebellar lesions, intracerebral hematomas, or myocardial infarction within 3 months of TIA or stroke. Also excluded were patients in whom the angiography revealed occlusion or tight stenosis of the internal carotid artery that made it impossible to measure rCBF with the intracarotid method.

Thirty-two men and 21 women were included (mean age, 64 years; range, 44 to 75 years). The six patients described in detail in this report were two men and four women (mean age, 66 years; range, 61 to 73 years) (Table 1). The protocol was approved by the Medical Faculty of the University of Copenhagen, Denmark.

Methods

All patients underwent the same examination procedures, including a full clinical neurological examination at the time of arrival to the hospital. Clinical examinations were repeated several times during the ward period. Cerebral angiography and rCBF measurements were performed within 12 to 24 hours after admission and in no case later than 48 hours after debut of the symptoms. A computed tomographic scan was carried out 1 day later and repeated after approximately 2 weeks and 6 months. The patients were examined for atrial fibrillation and previous myocardial infarction. Electrocardiography was performed in all.

Cerebral Angiography.—Puncture of the relevant common carotid artery was done using local anesthesia, and angiography of the carotid system and cerebral vessels was performed by administering the contrast medium through the cannula. The angiograms were inspected immediately. By the Seldinger technique, we introduced a small, soft, polyethylene catheter into the internal carotid artery after cerebral angiography.

rCBF Measurements.—Immediately after the cerebral angiography, we measured rCBF with the intracarotid xenon 133 injection technique.[1] Two hundred to 400 MBq of ^{133}Xe dissolved in 3 mL of saline was injected through the catheter, and for the following 2 minutes the clearance of isotope was recorded with a 254-detector gamma camera covering one hemisphere.[2] Each detector recorded radiation from approximately 1 cm^2 of the brain surface. Immediately after the isotope injection, each detector recorded the count rate with 1-second sampling intervals. The fast passage of high isotope concentrations through the carotid siphon and the middle and anterior cerebral arteries could be identified as vascular spikes in the clearance curve obtained with detectors covering these large vessels.[3] In the normal brain, vascular spikes occur within 1 to 3 seconds, and subsequently the isotope (blood) is distributed throughout the brain cortex. Here the maximum count rate plateau is obtained within

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Table 1.—Clinical Information on Group 2*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, y/sex	61/M	73/M	66/F	65/F	65/F	66/F
Hemisphere	R	L	R	R	R	R
Time to rCBF after start of symptoms, h	24	16	18	18	48	24
Symptoms before examination	3 attacks of 1-3 h L hemiparesis, confusion, aphasia, and dizziness over 14 d; admitted with 4th attack	3 attacks of R arm and leg weakness and paresthesias	Weakness L arm and leg	L facial paresthesia and weakness of L arm	Weakness L arm and leg	Weakness L arm and leg
Classification	Stroke	TIA	Stroke	TIA	TIA (stroke)	Stroke
Symptoms during examination	No further symptoms	New attack; transient R hemiparesis; confusion, 3-4 h	Confusion and full paresis L leg; 5-6 h	No symptoms	New attack; paresis L arm; paresthesias L side of face, 15-20 min	Aggravation of L hemiparesis; L-sided neglect, 24 h
Angiographically visible occlusions	None	None	Occlusion of parietal branch of MCA	None	None	None
CT scan	Low density R posterior crus of internal capsule	Normal; slight atrophy R parietal cortex	Low density R caudate nucleus	Normal	1st normal; 2nd and 3rd, low density R internal capsule	Low density R basal ganglia
Persisting symptoms after 6 mo	Slight movement disorder L arm	None	None	None	None	Slight movement disorder L arm

*rCBF indicates regional cerebral blood flow; TIA, transient ischemic attack; MCA, middle cerebral artery; and CT, computed tomography.

2 to 4 seconds after the bolus injection. Thus, the early isotope distribution and count rates can be used in evaluating the arterial distribution of blood.

For each detector, CBF (measured in milliliters per 100 g per minute) was calculated as the initial slope of the logarithmically transformed ^{133}Xe clearance curve obtained from 12 to 60 seconds after the bolus injection[4]: $CBF = k \times \lambda \times 100$, where k is the rate constant and λ is the tissue-to-blood partition coefficient for ^{133}Xe, which is 0.87 mL/g in gray matter. All data were automatically corrected for background activity and for clearance of the small amount of remaining isotope, which could be present when rCBF measurements were carried out with short intervals. There was a time interval of 15 to 20 minutes between the first and second measurements, and the following measurements were done with approximately 10-minute intervals. After computation, the data were visualized as a two-dimensional color picture of the lateral aspect of the brain (Fig 1), and the calculated values could be obtained from a printer (Fig 2). After the rCBF study, we examined the 254 clearance curves from each measurement. Simultaneously with each rCBF measurement, PCO_2, mean arterial blood pressure, and heart rate were recorded via the intracarotid catheter. The flow values were not corrected for PCO_2 changes in this study.

All repeated measurements were performed during a resting condition. Abnormal rCBF in a region was defined by the following criteria. A region should consist of at least 10 adjacent detectors representing approximately 10 cm^2 of the cortical surface. In the normal brain, the SD of the difference between repeated rCBF measurements in a 10-detector region is 3.3%.[5] We have chosen to define a hypoperfused region as 10 neighboring detectors each having at least a 20% lower rCBF value than found during the measurement when there were no symptoms and the rCBF pattern was evaluated to be normal. Therefore, mean rCBF in a hypoperfused region was at least five times beyond the expected SD in normal subjects. A hyperperfused region was defined as at least 10 adjacent detectors each recording rCBF increases of more than 40%. In this way, we minimized the risk that the focal blood flow increase was due to physiological activation, as 40% is more than twice the SD of the average focal activation response seen during pure intrinsic mental activity.[5]

RESULTS

rCBF Patterns and Angiography

When analyzing serial aspects of the rCBF patterns, we found a remarkably unsteady flow distribution in six patients. These rCBF patterns differed significantly from those of the remaining 47 patients. Therefore, the patients were considered belonging to two different groups, which we henceforth will refer to as groups 1 and 2.

Group 1.—In 47 patients, the rCBF patterns showed unaltered blood flow distribution during repeated measurements. If a region of focal hypoperfusion or hyperperfusion was present, this abnormality was found during all measurements. That is, the rCBF values and the localization and extension of the abnormally perfused regions were the same during all measurements. In this group, there was angiographic evidence of occlusions of the middle cerebral artery or peripheral branches from this artery in 23 patients. The angiography did not reveal signs of arterial occlusions or arterial spasms in 24 patients.

Group 2.—In six patients, the sequential rCBF measurements were completely different from those of group 1. In these six patients, the flow distribution was remarkably unsteady. During the examination, foci of hyperperfusion and hypoperfusion developed in different regions of the examined hemisphere. The calculated rCBF values and the extension of these abnormally perfused regions altered from measurement to measurement. They increased or decreased in size, and low or high mean blood flow was more or less pronounced. In case 2, it was only possible to carry out one measurement, as the patient felt great discomfort owing to the appearance of a new TIA. This patient was included in group 2 because a clearly abnormal rCBF pattern was associated with the appearance of neurological deficits and because the retrospective analysis of the clearance curves revealed that these were remarkably unstable. Figure 1 shows the changing rCBF patterns, and Fig 2 illustrates the localization and extension of the hyperperfused and hypoperfused regions. The global mean CBF is indicated in Table 2, and mean blood flow values in the affected regions are indicated in Table 3.

In five patients, the angiograms were

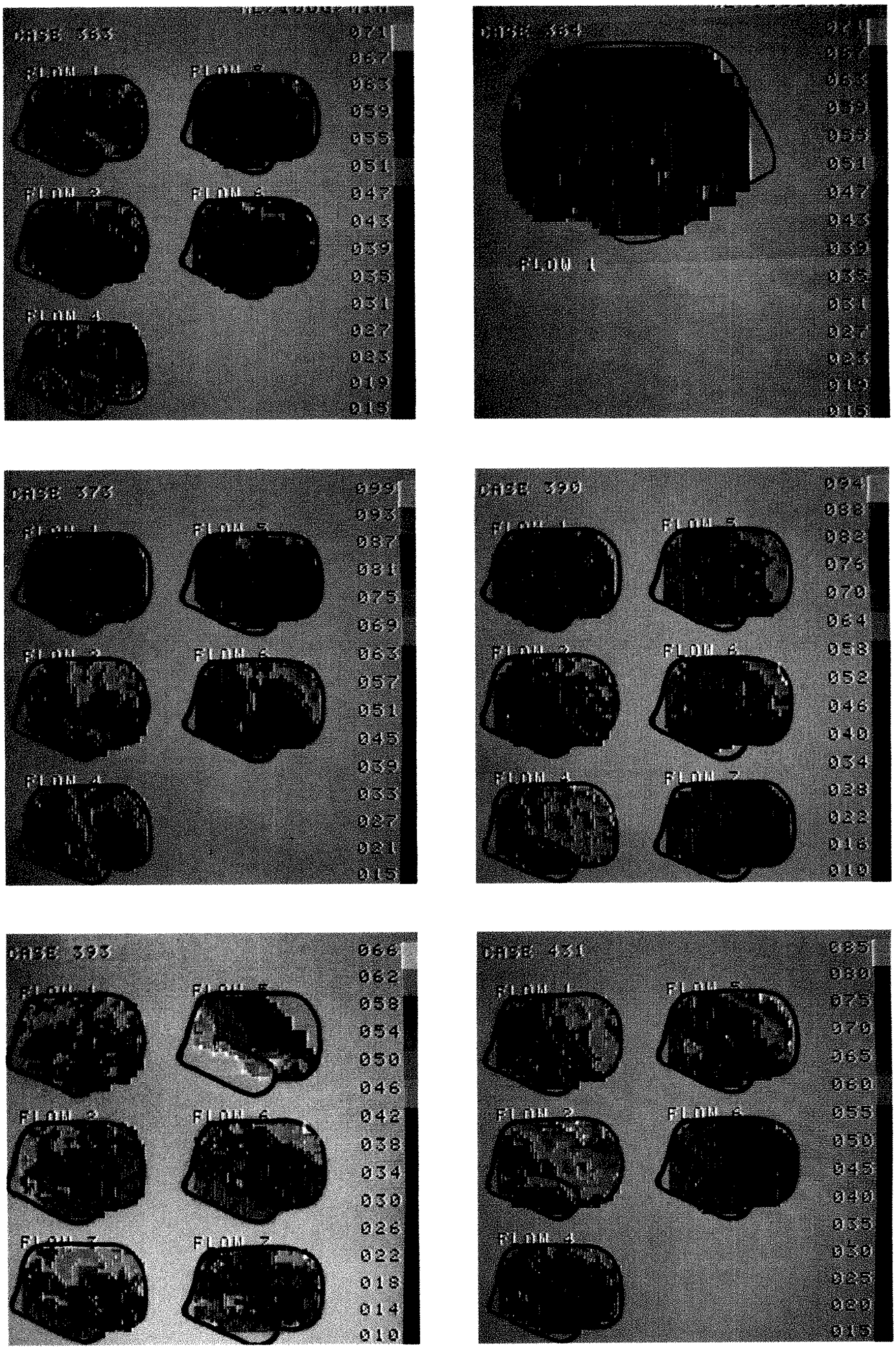

Fig 1.—Regional cerebral blood flow patterns from individual measurements. Color scale indicates blood flow in milliliters per 100 g per minute. Top left, Case 1; top right, case 2; center left, case 3; center right, case 4; bottom left, case 5; and bottom right, case 6.

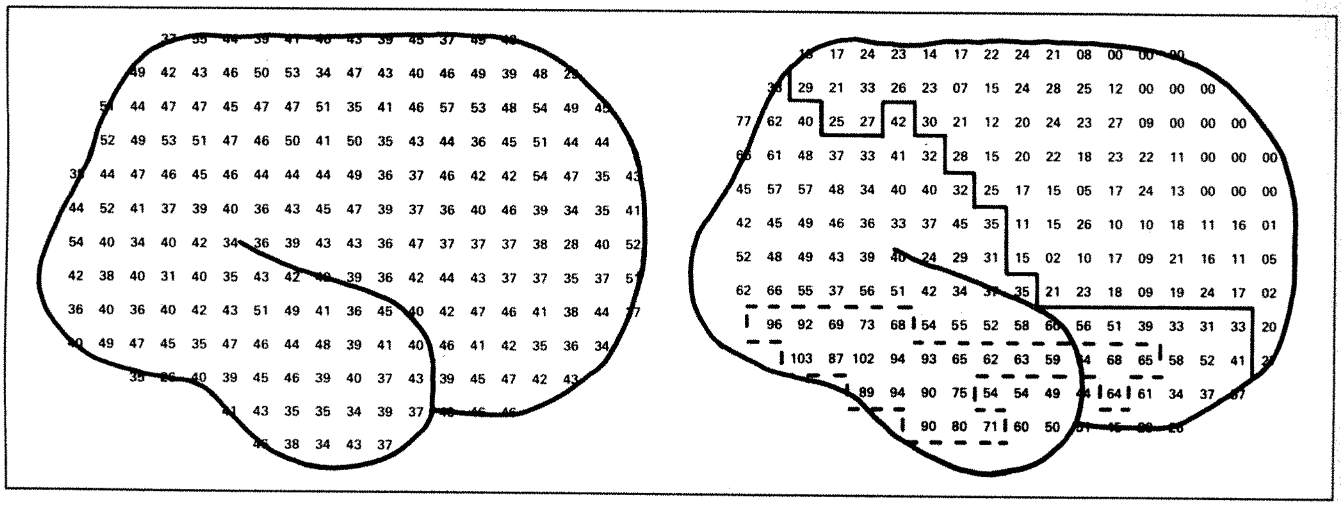

Fig 2.—An example of calculated mean regional cerebral blood flow (rCBF) values (in milliliters per 100 g per minute) as displayed on the printer (case 5). Each value represents data from one detector (1 cm²). During flow 1 (left), there was a normal rCBF distribution. During flow 5 (right), regions of hyperperfusion and hypoperfusion developed. The full line encircles the hypoperfused region, which includes values more than 20% below mean blood flow in unaffected brain regions. Broken line encircles the hyperperfused region, which includes values more than 40% above blood flow in unaffected brain regions. Note the gradually decreasing flow values when moving from high- to low-flow regions owing to the Compton scatter effect (see text).

without signs of arterial occlusions. In one patient (case 3), angiography failed to demonstrate a smaller parietal branch of the middle cerebral artery. One patient (No. 5) had slight hypertension (blood pressure, 170/100 mm Hg) and discrete angiographic signs of a small plaque in the right (relevant) internal carotid artery, just above the bifurcation. The patient was given antithrombotic therapy (warfarin [Coumadin] sodium) for 6 months. It cannot be ruled out that this slight pathological change in case 5 could have caused the symptoms. In none of the patients were there spasms of the arteries visible on the angiogram.

Isotope Arrival

The initial part of the plotted curves indicates the time of arrival of the isotope. In normally perfused brain tissue, a maximum count rate occurs 2 to 4 seconds after the bolus injection. Tight narrowing or occlusions of large arteries will cause an overdue arrival of the isotope.

Group 1.—There was a normal time of arrival in normally perfused brain regions. In regions of infarcts caused by vascular occlusions, maximum count rates were considerably delayed, two to three times later than in normally perfused regions. This was most marked in regions with cortical infarcts and less pronounced in regions overlying subcortical infarcts. Furthermore, vascular spikes were not recorded when an artery was occluded proximal to the location of the detector.

Group 2.—The initial part of the clearance curves from this group of patients showed a normal time of arrival of the isotope in all cortical regions irrespective of low, normal, or high blood flow being recorded from a region. An exception, however, was the delayed isotope arrival in a small subcortical infarct area in the parietal lobe of case 3.

Clinical Observations

In all patients, the degree of paresis was evaluated in accordance with the Medical Research Council score.

Group 1.—In this group, we observed no exacerbation of previous symptoms or development of new symptoms in connection with the examination.

Group 2.—Clinical symptoms are listed in Table 1. In two patients with stroke, there was aggravation of previous symptoms. In two patients with TIA, a new attack developed. All observed symptoms were transient, leaving no permanent sequelae. Two patients exhibited no exacerbation of previous symptoms or development of new symptoms. In none of the patients did headache develop.

Other Observations

During the rCBF measurements, blood pressure, heart rate, and P_{CO_2} were within the normal range. There was no history of cardiac disease in the six patients of group 2. In all cases, the electrocardiogram showed normal sinus rhythm, and there were no signs of atrioventricular block, hypertrophy, or other types of cardiac abnormalities. In none of the patients were there clear indications as to a direct known cause of TIA or stroke. They did not receive any kind of acute medical or surgical therapy. After discharge from the hospital, the patients returned for ambulatory visits regularly for the following 6 months. During this period, the patients' conditions seemed to be fairly stable. One month after the examination, patient 4 experienced one TIA lasting 10 minutes. In patient 3, postinfarct epilepsy developed, and the patient had two generalized seizures within the observation period. In the remaining four patients, there were no clinical signs of further attacks. There were no clinical signs of improvement of the persisting symptoms in patients 1 and 6 (Table 1).

COMMENT

The observation of development of pronounced focal hypoperfusion suggests that focal ischemia due to arteriolar spasms was able to be elicited in the six patients of group 2 on whom we will focus this discussion.

Most likely, the severity and duration of neurological symptoms, associated with the presence of cerebrovascular instability, are proportional to the number and duration of periods during which ischemic flow values are present, as well as to the degree of flow reduction. The magnitude of the flow reduction was not uniform in the unstable perfused regions, that is, some areas within these regions were more severely affected than others (Fig 1).

The transient aggravation of motor and sensory deficits observed during and after the examination of four of the patients described herein were most likely due to transient ischemia in the corresponding motor and sensory zones.[5] The cortical neuronal function might also have been affected by is-

Table 2.—Mean Hemispheric CBF and Paco$_2$ During Individual Measurements*

Patient No.	Flow No.	Mean Hemispheric CBF, mL · 100 g^{-1} · min^{-1}	Paco$_2$, mm Hg
1	1	44	41.6
	2	41	39.7
	3	26†	32.1
	4	47	40.2
	5	40	41.2
	6	38	41.1
2	1	38	45.1
3	1	55	44.3
	2	63	44.5
	3	37†	35.4
	4	62	43.1
	5	50	43.5
	6	52	43.3
4	1	49	40.6
	2	54	40.2
	3	30†	27.1
	4	64	41.7
	5	54	41.2
	6	48	39.2
	7	44	38.2
5	1	42	37.1
	2	39	35.5
	3	42	36.2
	4	29†	28.2
	5	44	33.4
	6	40	35.7
	7	39	35.2
6	1	56	40.8
	2	63	41.9
	3	37†	32.9
	4	50	37.8
	5	55	41.1
	6	44	40.9

*CBF indicates cerebral blood flow.
†Cerebral blood flow study during voluntary hyperventilation.

Table 3.—Lowest and Highest rCBF Values Measured in Affected Regions*

	Hypoperfused Regions		Hyperperfused Regions	
Patient No.	rCBF	No. of Detectors	rCBF	No. of Detectors
1	30 (25-35)	41	61 (50-67)	15
2	19 (16-28)	25	...	...
3	26 (16-34)	36	82 (77-91)	25
4	26 (11-37)	38	90 (73-102)	20
5	13 (0-28)	98	85 (69-102)	13
6	36 (30-40)	52	80 (67-92)	20

*rCBF indicates regional cerebral blood flow, measured in milliliters per 100 g per minute. Values are mean (range).

chemia in the two patients who did not exhibit detectable neurological deficits in association with the examination. Insufficient function of cortical areas outside motor and sensory zones may not have been detected if the effect was transient and mild.

Ischemic Threshold

In this study, we refer to the ischemic threshold, defined as the level at which normal neuronal function of the cerebral cortex is affected owing to insufficient blood perfusion. This threshold has been determined to be around 23 m·100 g^{-1}·min^{-1}.[7-10] In our study, we calculated mean rCBF from 48-second intervals. In the hypoperfused regions, mean rCBF was found to be from 13 to 36 mL·100 g^{-1}·min^{-1}. However, these values are considerably overestimated owing to scattered radiation (Compton scatter) in low-flow regions originating from normal or highly perfused surroundings. Olsen et al[11,12] have shown that about 50% of the radiation recorded from the developed low-flow areas is scattered radiation. Therefore, the actual average blood flow in the low-flow areas most likely is around or below the ischemic threshold. As the Compton scatter effect is of greatest importance in low-flow regions close to normal or highly perfused regions, it is not possible to determine the exact extension of a low-flow area. The borders are blurred, and measured flow values are successively decreased from high- to low-flow regions. This is illustrated in Fig 2.

It is not likely that the decrease of blood flow was due to primary physiological deactivation, as complete pharmacological inhibition of the total hemisphere (which excludes Compton effect) only reduces blood flow down to the baseline level, around 22 mL·100 g^{-1}·min^{-1}.[13]

Arteriolar Spasms and Significance of Cerebrovascular Instability

Cerebral angiography did not reveal signs of large-vessel occlusions or spasms of the arteries visible on angiography in the six patients herein described. In one patient (case 3), there was occlusion of a small parietal branch of the middle cerebral artery, and the computed tomographic scan revealed a small subcortical parietal infarct. However, in this case, the abnormally perfused regions were much more widespread than the extension of the infarct area. Most of the frontal lobe and some of the temporal and parietal lobes were affected.

During all rCBF measurements, there were normal temporal and spatial isotope distribution in the territories of the main brain arteries.[3] The isotope angiograms[14] were without signs of occlusions, except in the small infarct area of case 3. We believe that the combination of the fluctuating extension of focal hyperperfused and hypoperfused regions and the absence of signs of occlusion on the arteriogram and isotope angiograms can exclude occlusions of major arteries.

Recently, a condition of cerebrovascular tone instability has been defined as transient spasms of the arterioles alternating with normal calibration of these vessels and/or short periods of vasodilation.[15,16] When arteriolar spasms are present, the blood flow decreases to values consistent with ischemic levels. It is likely that regulation of vascular tone is beyond normal control in the affected, abnormally perfused regions. It was suggested that the arteriolar spasms must be considered the primary event, and the vasodilation causing episodes of hyperemia may be posthypoxic vasodilation or an overshot by compensating mechanisms. The examination procedures used herein, ie, carotid puncture, indwelling catheter, and intracarotid bolus injections, are known to be able to induce the development of focal cerebral hypoperfusion, transient focal ischemia, and a migraine attack in patients suffering from classic and hemiplegic migraine.[15-18] The exact mechanism of this phenomenon is not known. Most likely, the vascular changes in the patients with TIA and stroke reported herein also were triggered of by one or several of the procedures performed in connection with the cerebral angiography and rCBF measurements.

Repeated bolus injections of contrast medium, isotope solution, and heparinized saline might be a strong provocative factor causing release of vasoactive substances from platelets, endothelium, or perivascular nerves. Mowat et al[19] have reported that a few seconds after a bolus of saline or ^{133}Xe solution was injected into the renal artery of healthy dogs, a drastic fall in renal blood flow was observed. Most likely this was due to transient constriction on the afferent arteriolar level. The eliciting of a similar arterio-arteriolar reflex in the vessels supplying the brain could be the primary provoking factor of arteriolar spasms and cerebrovascular instability. Another possible provoking factor might be release of vasoactive substances, such as serotonin, from mechanically damaged platelets. However, the characteristic flow changes reported herein only seem able to be provoked in subjects who are hypersensitive to the triggering factor(s), that is, in patients suffering from classic and hemiplegic migraine and apparently in a group of patients with TIA and stroke as reported here.

Cerebrovascular Instability: Consequence or Cause of TIA and Stroke

The unstable blood flow regulation observed might be a consequence of previous ischemic accidents. However, it was only observed in these six patients, who had no obvious thromboembolic sources, and not in the rest of the examined patients. It might be possible that the condition of cerebrovascular instability also was present during previous spontaneous attacks of transient focal ischemia in these six patients. In our material, the incidence of cerebrovascular instability able to be provoked was found in six (11%) of 53 patients with TIA and stroke without a history of migraine. This incidence could be considered the normal occurrence of hypersensitive subjects in the population. However, this is probably not the case. It has been reported that development of neurological symptoms in connection with intracarotid angiography and rCBF measurements only occurred with an overall rate of 1.3% in nearly 4000 patients examined for a variety of diseases.[20] Therefore, it is likely that the occurrence rate of hypersensitive subjects among patients with TIA and stroke is much higher than normally found in the population as a whole. According to our experience, the highest incidence of hypersensitive subjects is probably found in the group of patients suffering from classic and hemiplegic migraine, in which cerebrovascular instability and transient neurological deficits are able to be provoked in approximately 60% to 70% of cases. Although the recovery from a vascular migraine attack generally is complete, there are reports indicating that permanent neurological sequelae can develop in connection with an attack.[12,21-23] Furthermore, Fisher[24,25] has suggested that migraine accompaniments can cause otherwise unexplained TIA.

It seems likely that attacks of cerebrovascular instability can occur spontaneously in hypersensitive patients, as the provoked symptoms usually are exactly like those experienced during spontaneous attacks. Vasoconstrictor-induced focal cerebral ischemia might be associated with or even the cause of TIA and stroke in patients who have a normal angiographic and cardiac status. On the other hand, abnormal angiography or the finding of cardiac disease does not exclude the coexistence of hypersensitivity to vasospastic stimuli. It should also be considered that a disposition for episodes of cerebrovascular instabilty might be a cause of a previous ischemic event. This might partly explain the unstable clinical condition and fluctuation of neurological deficits seen in some patients with stroke and TIA after a focal cerebral ischemic event.

References

1. Høedt-Rasmussen K, Sveinsdottir E, Lassen NA. Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circ Res.* 1966;18:237-247.
2. Sveinsdottir E, Larsen B, Rommer P, Lassen NA. A multi-detector scintillation camera with 254 channels. *J Nucl Med.* 1977;18:168-174.
3. Friberg L, Olsen TS, Roland PE, Paulson OB, Lassen NA. Focal increase of blood flow in the cerebral cortex of man during vestibular stimulation. *Brain.* 1985;108:609-623.
4. Olesen J, Paulson OB, Lassen NA. Regional cerebral blood flow in man determined by initial slope of the clearance of intra-arterially injected Xe-133. *Stroke.* 1971;2:519-540.
5. Lassen NA, Roland PE, Larsen B, Melamed E, Soh K. Mapping of human cerebral functions: a study of the regional cerebral blood flow pattern during rest, its reproducibility, and the activations seen during basic sensory and motor functions. *Acta Neurol Scand.* 1977;64(suppl):262-263.
6. Friberg L, Roland PE. Functional activation and inhibition of regional cerebral blood flow and metabolism. In: Olesen J, Edvinsson L, eds. *Basic Mechanisms of Headache.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1988:89-98.
7. Trojaborg W, Boysen G. Relation between EEG, regional cerebral blood flow and internal carotid pressure during carotid endarterectomy. *Electroencephalogr Clin Neurophysiol.* 1973; 34:61-69.
8. Powers WJ, Grabb RL, Raichel ME. Pathophysiological responses to focal cerebral ischemia in humans. *Ann Neurol.* 1984;16:546-552.
9. Heiss WD, Hayakawa T, Watz AG. Cortical neuronal function during ischemia: effects on occlusion of one middle cerebral artery on single unit activity in cats. *Arch Neurol.* 1976;33:813-820.
10. Jones TH, Morawetz RB, Crowell RM, et al. Thresholds of focal cerebral ischemia in awake monkeys. *J Neurosurg.* 1981;54:773-782.
11. Olsen TS, Larsen B, Skriver EB, Enevoldsen E, Lassen NA. Focal cerebral ischemia measured by the intra-arterial ^{133}xenon method: limitations of 2-dimensional blood flow measurements. *Stroke.* 1981;12:736-746.
12. Olsen TS, Friberg L, Lassen NA. Ischemia may be the primary cause of the neurological deficits in classic migraine. *Arch Neurol.* 1987;44:156-161.
13. Roland PE, Friberg L. The effect of the GABA-A agonist THIP on regional cortical blood flow in humans: a new test of hemispheric dominance. *J Cereb Blood Flow Metab.* 1988;8:314-323.
14. Olsen TS, Larsen B, Skriver EB, Herning M, Enevoldsen E, Lassen NA. Focal cerebral hyperaemia in acute stroke: incidence, pathophysiology and clinical significance. *Stroke.* 1981;12:598-607.
15. Friberg L, Olsen TS, Roland PE, Lassen NA. Focal ischemia caused by instability of cerebrovascular tone during attacks of hemiplegic migraine: a regional cerebral blood flow study. *Brain.* 1987;110:917-934.
16. Friberg L, Olsen TS. Rapid extreme oscillations of focal cerebral blood flow during the aura phase of migraine. In: Rose FC, ed. *New Advances in Headache Research.* London, England: Smith-Gordon & Co Publishers; 1989:163-167.
17. Janzen R, Tanzer A, Zschocke S, Dieckmann H. Postangiographische Spätreaktionen der Hirngefässe bei Migräne-Kranken. *Z Neurol.* 1972; 201:24-42.
18. Friberg L, Olsen TS, Lassen NA. Cerebrovascular tone instability causing focal ischemia. In: Nobin A, Owman C, Arneklo-Nobin B, eds. *Neuronal Messengers in Vascular Function.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1987:549-556.
19. Mowat P, Andrei NL, Maxwell MH. Limitations of ^{133}Xe washout technique in estimation of renal blood flow. *Am J Physiol.* 1972;223:682-688.
20. Ingvar DH, Lassen NA. Cerebral complications following measurements of regional cerebral blood flow (rCBF) with the intra-arterial ^{133}xenon injection method. *Stroke.* 1973;4:658-665.
21. Connor RCR. Complicated migraine. *Lancet.* 1962;1:1072-1075.
22. Boisen E. Strokes in migraine: report on seven strokes associated with severe migraine attacks. *Dan Med Bull.* 1975;22:100-106.
23. Rothrock JF, Walicke P, Swenson MR, Lyden PD, Logan WR. Migrainous stroke. *Arch Neurol.* 1988;45:63-67.
24. Fisher CM. Late-life migraine accompaniments as a cause of unexplained transient ischemic attacks. *Can J Neurol Sci.* 1980;7:9-12.
25. Fisher CM. Late-life migraine accompaniments: further experience. *Stroke.* 1986;17:1033-1042.

Gangliosides in Cerebrospinal Fluid in 'Probable Alzheimer's Disease'

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• The concentrations of the four major brain gangliosides—GM$_1$, GD$_{1a}$, GD$_{1b}$, and GT$_{1b}$—were determined in cerebrospinal fluid from 43 patients with "probable Alzheimer's disease" and 19 healthy controls. Alzheimer's disease was divided into type I (with the memory disturbances and predominant cortical parietal symptoms that are characteristic of Alzheimer's disease) and type II (with general cognitive and mild confusional symptoms, with or without only mild parietal symptoms). The GM$_1$ concentration was significantly higher in patients with Alzheimer's disease type I than in those with Alzheimer's disease type II and age-matched controls, but did not differ significantly between patients with Alzheimer's type II and age-matched controls. As gangliosides are enriched in nerve cell membranes, preferentially in synapses, the findings suggest more severe degeneration of cortical nerve cells in patients with Alzheimer's disease type I than in those with Alzheimer's disease type II.

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Alzheimer's disease (AD) is characterized by progressive dementia with memory disturbances and, in typical cases, cortical parietal symptoms.[1-3] The traditional neuropathologic findings in patients with AD consist of degeneration of the cerebral cortex, with a marked loss of neurons and an increased number of senile plaques and neurofibrillary tangles compared with nondemented individuals of the same age.[4-8]

In previous studies in our department, it has been suggested that among patients fulfilling the NINCDS-ADRDA criteria for "probable AD,"[9] two subgroups of patients can be delimited based on their clinical symptoms: AD type I and AD type II.[10-13] Alzheimer's disease type I is characterized by the classic cortical temporoparietal symptoms, low age at onset, low frequency of concomitant vascular diseases, normal blood-brain barrier function, and low frequency of white-matter lesions and has, therefore, been suggested to constitute "classic" or "pure" AD.[10-13] Alzheimer's disease type II is characterized by less cortical and more generalized symptoms of general cognitive and confusional symptoms, high age at onset, high frequency of concomitant vascular diseases, mildly impaired blood-brain barrier function, and high frequency of white-matter lesions, suggesting that a combination of relatively mild Alzheimer encephalopathy, age-related changes, and vascular changes (disease of small blood vessels with white-matter lesions) may be involved in the pathogenesis of dementia, ie, in the production of dementia symptoms, in patients with AD type II.[10-13]

Gangliosides are sialic acid–containing glycosphingolipids that are present in all cells of the body.[14] The concentration of gangliosides is highest in the brain; in the cerebral cortex, it is about three to five times as high as in the white matter.[15-17] The four major gangliosides—GM$_1$, GD$_{1a}$, GD$_{1b}$, and GT$_{1b}$—have been found to be most abundant in the nerve endings (synaptosomes),[18,19] and particular enrichment of the ganglioside GM$_1$ has been demonstrated in the synaptic junction.[20] The gangliosides are located in the outer layer of the plasma membrane[14] and are, to a certain extent, released into the intercellular space in the course of the normal cell surface turnover, a process called "cell surface shedding."[21] Because the intercellular space is in direct contact with the cerebrospinal fluid (CSF),[22] the shedding of gangliosides is reflected in the CSF.[23]

In diseases like AD, which are characterized by progressive degeneration of neurons, an increased release of gangliosides into CSF can be expected. Therefore, we decided to investigate CSF for its content of gangliosides in AD and to evaluate their use as indexes of neuronal degeneration and as biologic markers of AD.

PATIENTS, SUBJECTS, AND METHODS

Patients

Forty-three patients with probable AD[9] were included in the study (15 men and 28 women; 54 to 87 years of age; mean ± SD age, 71.3 ± 8.2 years). All patients underwent a thorough clinical investigation, including a medical history, physical examination, neurologic and psychiatric examinations, screening laboratory tests, electrocardiography, chest roentgenography, electroencephalography, and computed tomography of the brain. Patients with a history of major psychiatric or neurologic disorders, alcoholism, or major head trauma were excluded, as were those with manifest or suspected other primary (eg, Pick's disease, Parkinson's dis-

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Table 1.—Gangliosides in Cerebrospinal Fluid in Alzheimer's Disease (AD) Type I and Type II and in Age-Matched Controls*

Ganglio-sides	AD Type I (n = 12)	Younger Controls (n = 10)	AD Type II (n = 10)	Older Controls (n = 9)
GM$_1$	32.8 ± 14.7	12.0 ± 3.3	14.2 ± 5.9	10.3 ± 4.5
GD$_{1a}$	34.8 ± 27.1	21.6 ± 7.4	26.8 ± 13.0	19.9 ± 8.6
GD$_{1b}$	21.9 ± 14.5	25.0 ± 12.9	16.3 ± 6.7	20.0 ± 11.6
GT$_{1b}$	30.8 ± 24.4	37.4 ± 16.4	26.6 ± 13.8	37.3 ± 16.0
Total	**120.3 ± 68.6**	**96.0 ± 29.9**	**83.9 ± 31.7**	**87.6 ± 34.2**

*Values are given as mean ± SD nanomoles per liter. Total is equal to GM$_1$ + GD$_{1a}$ + GD$_{1b}$ + GT$_{1b}$. For AD type I vs AD type II, $P < .001$; for AD type I vs younger controls, $P < .0001$.

Table 2.—Gangliosides in Cerebrospinal Fluid in 'Probable Alzheimer's Disease' and in Age-Matched Controls*

Ganglio-sides	"Probable AD" (n = 43)	Controls (n = 19)
GM$_1$†	25.6 ± 14.6	11.2 ± 3.9
GD$_{1a}$‡	39.0 ± 26.5	20.8 ± 7.8
GD$_{1b}$	22.2 ± 11.4	22.6 ± 12.2
GT$_{1b}$§	29.4 ± 17.7	37.4 ± 15.8
Total	**116.2 ± 58.0**	**92.0 ± 31.4**

*Values are given as mean ± SD in nanomoles per liter. Total is equal to GM$_1$ + GD$_{1a}$ + GD$_{1b}$ + GT$_{1b}$.

†"Probable AD" vs controls, $P < .0001$.

‡"Probable AD" vs controls, $P < .005$.

§"Probable AD" vs controls, $P < .05$.

ease, and progressive supranuclear palsy) or secondary (eg, depression, metabolic disturbances, and toxic effects) causes of dementia. Patients with a history of transient ischemic attacks or stroke episodes, occurrence of pronounced vascular factors, or computed tomographic scan findings of infarcts were also excluded. Thus, the diagnosis of "probable AD" was made in accordance with the NINCDS-ADRDA criteria,[9] ie, after the exclusion of all other known disorders that could account for the dementia.

The patients fulfilling the NINCDS-ADRDA criteria for "probable AD"[9] were divided into two groups—AD type I and AD type II—based on their clinical symptoms.[10,11] The AD type I group consisted of five men and seven women, aged 54 to 72 years, with a clinical picture of memory disturbances together with predominant cortical parietal symptoms, while the AD type II group consisted of three men and seven women, aged 69 to 87 years, with memory disturbances, general cognitive symptoms, and mild confusional symptoms, but with absence of or only mild parietal symptoms.[10,11] The importance of adequate matching for severity of dementia in studies concerning clinical symptoms in demented patients has been emphasized, as the prevalence of brain regional symptoms is dependent on the severity of dementia,[24] ie, parietal symptoms may be absent in mildly demented patients.[1-3,10] For this reason, mildly demented patients were excluded from the AD type I and AD type II groups. All clinical diagnoses and assessments of clinical symptoms were made without knowledge of the results of the analyses of the ganglioside concentrations in CSF and vice versa.

Controls

The controls included 13 men and six women, aged 55 to 77 years, admitted for minor surgery (ie, coxarthrosis and prostate hyperplasia) involving spinal anesthesia. No controls had histories, symptoms, or signs of psychiatric or neurologic disease, malignant disease, or systemic disorders (eg, rheumatoid arthritis and infectious disease). The cognitive status was evaluated using the Mini-Mental State examination.[25] Individuals with scores below 28 were excluded.

As we had found low negative correlations between CSF gangliosides and age in a larger control sample with an age range of 18 to 85 years (unpublished data), the control group was divided into one younger and one older group for age matching with the AD type I and AD type II groups. However, in the control group in this study (n = 19; 51 to 77 years of age), no significant correlations were found between CSF gangliosides and age (data not shown) and no significant differences were found in CSF gangliosides between the younger and older control groups (Table 1).

Methods for CSF Analysis

Lumbar punctures were performed in the L3-4 or L4-5 interspace. A volume of 12 mL of CSF was collected in silicone-coated tubes and gently mixed to avoid gradient effects. A blood sample was taken at the same time. All CSF samples with more than 500 erythrocytes per microliter were excluded.

Quantitative determination of albumin in serum and CSF was performed by rocket immunoelectrophoresis.[26] The albumin ratio (CSF albumin [in milligrams per liter] divided by serum albumin [in grams per liter]) was used as the measure of the blood-brain barrier function.[27]

Concentrations of gangliosides GM$_1$, GD$_{1a}$, GD$_{1b}$, and GT$_{1b}$ were individually determined with an anticholera toxin B subunit monoclonal antibody after chromatography and sialidase hydrolysis of GD$_{1a}$, GD$_{1b}$, and GT$_{1b}$ to GM$_1$ and incubation with cholera toxin B subunit on high-performance, thin-layer plates.[28] The sensitivity of this method is 50 fmol of GM$_1$ per liter, the within-run imprecisions are 7% to 9%, and the between-run imprecisions are 12% to 14%.[28] The binding of cholera toxin to ganglioside GM$_1$ is highly specific.[29] The production and the specificity of the monoclonal antibody to cholera toxin B subunit have been described previously.[30]

Statistical Analysis

For comparisons between groups, the Wilcoxon two-sample test was used for quantitative parameters and the χ^2 test for qualitative parameters. The Spearman Rank Correlation Coefficient was used for correlations.

The study was approved by the Ethics Committee of the University of Göteborg, Sweden. The patients with AD (or their nearest relatives) and the controls gave their informed consent to participate in the study.

RESULTS

The mean age did not differ significantly between patients with "probable AD" (n = 43; mean ± SD age, 71.3 ± 8.2 years) and controls (n = 19; mean ± SD age, 67.2 ± 8.5 years), between patients with AD type I (n = 12; mean ± SD age, 64.8 ± 5.3 years) and younger controls (n = 10; mean ± SD age, 61.3 ± 7.3 years), or between patients with AD type II (n = 10; mean ± SD age, 78.0 ± 6.1 years) and older controls (n = 9; mean ± SD age, 73.8 ± 2.0 years). The severity of dementia did not differ between patients with AD type I and AD type II, as the groups were matched for this variable (see "Patients, Subjects, and Methods" section). The duration of dementia did not differ significantly between patients with AD type I (6.8 ± 2.4 years) and AD type II (5.2 ± 3.0 years).

No significant correlations were noted between the albumin ratio and the total CSF ganglioside concentration in patients with "probable AD" ($r = -.08$) or in controls ($r = .07$), nor did any of the four individual brain gangliosides show significant correlations with the albumin ratio (data not shown).

The mean concentrations of gangliosides in patients with probable AD and controls are shown in Table 2. The total concentration of the four brain gangliosides were not found to differ significantly, but there was a changed proportion of gangliosides between the groups: there was an increase in GM$_1$ (222%; 25.6 for "probable AD" vs 11.2 for controls) and GD$_{1a}$ (188%; 39.0 for "probable AD" vs 20.8 for controls) compared with controls, while GT$_{1b}$ was decreased (79%; 29.4 for "probable AD" vs 37.4 for controls).

When patients with AD type I and age-matched controls were compared, the difference in the GM$_1$ concentration was even more pronounced (273%; 32.8 for AD type I vs 12.0 for controls), while the difference in the GD$_{1a}$ concentration did not reach statistical significance (161%; 34.8 for AD type I vs 21.6 for controls) (Table 1). GD$_{1b}$ concentration, GT$_{1b}$ concentration, or the total concentration of the four gangliosides did not

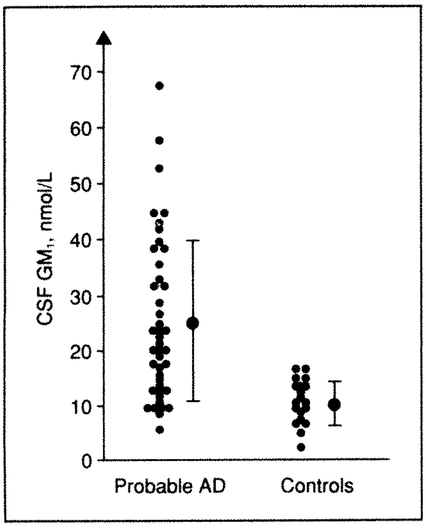

Fig 1.—Individual and mean ± SD (vertical bars) values for cerebrospinal fluid (CSF) GM_1 concentration in patients with "probable Alzheimer's disease" (AD) and age-matched controls. "Probable AD" vs controls, $P < .0001$.

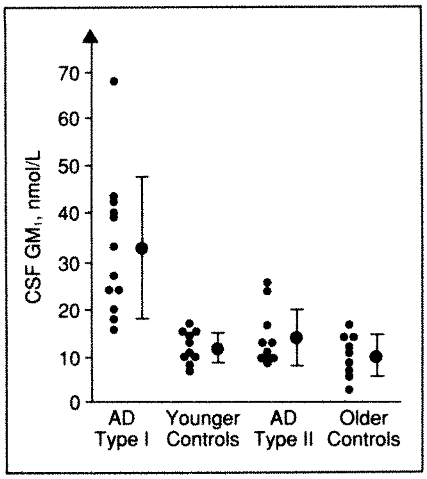

Fig 2.—Individual and mean ± SD (vertical bars) values for cerebrospinal fluid (CSF) GM_1 in patients with Alzheimer's disease (AD) type I, AD type II, and age-matched controls. Patients with AD type I vs younger controls, $P < .0001$; patients with AD type I vs patients with AD type II, $P < .001$; and patients with AD type II vs older controls and younger controls vs older controls, not significant.

differ significantly. The GM_1 concentration was also significantly higher in patients with AD type I compared with those with AD type II (231%; 32.8/14.2), while GD_{1a}, GD_{1b}, GT_{1b}, and the total concentration of the four gangliosides did not differ significantly. No significant differences in CSF gangliosides were noted between patients with AD type II and age-matched controls.

Figures 1 and 2 show the individual GM_1 values. Most (65%; 28/43) patients with probable AD had higher GM_1 values than controls, but there was substantial overlap, as 15/43 (35%) of patients with "probable AD" had GM_1 values that were within the range of the control values (Fig 1). In the AD type I group, one of 12 patients had a GM_1 value that was within the range of control values (Fig 2). In contrast, eight (80%) of 10 patients with AD type II had GM_1 values that were within the range of control values (Fig 2).

COMMENT

Only recently have methods been developed to investigate ganglioside concentrations in the CSF of individual patients.[23,28] Consequently, the potential of CSF gangliosides to reflect changes in the central nervous system ganglioside metabolism and degeneration of ganglioside-rich membranes has not been fully established. Several studies, however, have suggested that CSF gangliosides are derived from the central nervous system by shedding and thus reflect the release of gangliosides from brain plasma membranes.[23,28,31] The absence, found in our study, of a correlation between the major CSF gangliosides and albumin ratio supports the conclusion that these gangliosides are predominantly derived from the central nervous system and not from the serum. This is further supported by the finding of a different ganglioside pattern in serum than in CSF.[32]

Our study revealed changes in CSF ganglioside concentrations in patients with probable AD. Compared with controls, a marked increase was noted in GM_1 and GD_{1a} concentrations. The increase in GM_1 concentration mainly occurred in patients with AD type I, while the mean GM_1 value for patients with AD type II did not differ significantly from that for age-matched controls. These findings support the relevance of the division of "probable AD" into two types.

The concentration of gangliosides is three to five times as high in the cortex as in the white matter.[15-17] The brain gangliosides are preferentially located to neurons,[14,33,34] but their subcellular location in the neurons is insufficiently known. Some investigators claim that the four major gangliosides—GM_1, GD_{1a}, GD_{1b}, and GT_{1b}—are most abundant in the nerve endings (synaptosomes),[18,19] while others claim that they are distributed over a major portion of the neuronal surface.[34,35] Among the brain gangliosides, the concentrations of GM_1 and GD_{1a} are known to increase during the phase of outgrowth of axons and synaptogenesis in the development of the brain, suggesting a relation between synapses and GM_1 and GD_{1a} gangliosides.[36] GM_1 has also been shown to be enriched in the synaptic junction.[14,20] Thus, one possible explanation for the increase in GM_1 and GD_{1a} concentrations may be that it reflects the severe degeneration of cortical nerve cells and synapses in "probable AD," preferentially in the (younger) AD type I group. Several postmortem studies have shown that the cortical neuronal loss is greater in younger than in older patients with AD.[8,37-39] However, the increase in CSF GM_1 concentration in the younger AD type I group is not attributable to age differences, as no difference in CSF GM_1 was noted between the older and younger control groups and no increase in the older AD type II group compared with age-matched controls. The difference in CSF GM_1 concentration between the AD type I and AD type II groups is not caused by different severity of dementia, as the groups were matched for this parameter (see "Patients, Subjects, and Methods" section).

Among the gangliosides, GM_1 was found to have the highest discriminative capacity between groups. Although the GM_1 concentration was considerably higher in patients with "probable AD" than in controls, there was substantial overlap (Fig 1). However, the concentration of GM_1 in CSF discriminated patients with AD type I from controls, as well as from patients with AD type II: only one (10%) of 10 controls and two (20%) of 10 patients with AD type II had CSF GM_1 values within the range of the AD type I group. These findings suggest that GM_1 may be a biologic marker of pure AD (AD type I). Further studies are needed to elucidate the potential of CSF GM_1 concentration as a biologic marker for AD type I. Our intention is to further investigate its sensitivity in studies on larger patient and control samples and its specificity in studies including patients with diseases, such as Pick's disease, that are also characterized by neuronal and synaptic degeneration. Preliminary results of studies on vascular dementia reveal low CSF GM_1 values, comparable with those in patients with AD type II and in controls.

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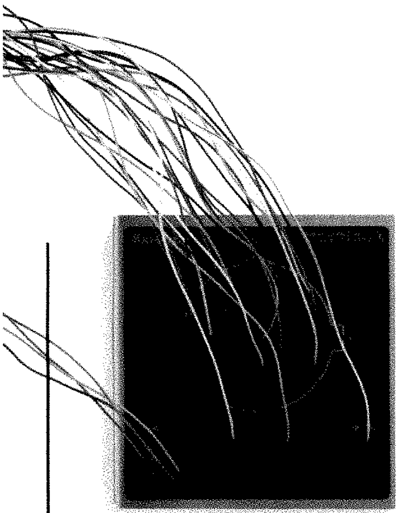
References

1. Sjögren T, Sjögren H, Lindgren Å. Morbus Alzheimer and morbus Pick: a genetic, clinical and patho-anatomical study. *Acta Psychiatr Neurol Scand.* 1952;(suppl 82):66-115.
2. Gustafson L. Differential diagnosis with special reference to treatable dementias and pseudodementia conditions. *Dan Med Bull.* 1985;32(suppl 1):55-59.
3. Lishman WA. *Organic Psychiatry: The Psychological Consequences of Cerebral Disorder.* 2nd ed. St Louis, Mo: Mosby–Year Book Medical Publishers; 1987.
4. Kemper T. Neuroanatomical and neuropathological changes in normal aging and in dementia. In: Albert ML, ed. *Clinical Neurology of Aging.* New York, NY: Oxford University Press; 1984:9-52.
5. Tomlinson BE, Corsellis JAN. Ageing and the dementias. In: Hume Adams J, Corsellis JAN, Duchen LW, eds. *Greenfield's Neuropathology.* London, England: Edward Arnold Publishers; 1984:951-1025.
6. Mann DMA. The neuropathology of Alzheimer's disease: a review with pathogenetic, aetiological and therapeutic considerations. *Mech Ageing Dev.* 1985;31:215-255.
7. Terry RD. Alzheimer's disease. In: Davies RL, Robertson DM, eds. *Textbook of Neuropathology.* Baltimore, Md: Williams & Wilkins; 1985:824-841.
8. Coleman PD, Flood DG. Neuron numbers and dendrite extent in normal aging and Alzheimer's disease. *Neurobiol Aging.* 1987;8:521-545.
9. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology.* 1984;34:939-944.
10. Blennow K, Wallin A, Gottfries CG. Presence of parietal lobe symptomatology distinguishes early and late onset Alzheimer's disease. *Int J Geriatr Psychiatry.* 1991;6:147-154.
11. Blennow K, Wallin A, Gottfries CG. Confusional symptomatology distinguishes early- and late-onset Alzheimer's disease. *Aging.* 1990;2:395-401.
12. Blennow K, Wallin A, Uhlemann C, Gottfries CG. White-matter lesions on CT in Alzheimer patients: relation to clinical symptomatology and vascular factors. *Acta Neurol Scand.* 1991;83:187-193.
13. Blennow K. *Heterogeneity of Alzheimer's Disease.* (Doctoral thesis). Göteborg, Sweden: Department of Psychiatry and Neurochemistry, University of Göteborg; 1990. Doctoral thesis. ISBN 91-628-0125-2.
14. Svennerholm L. Structure and biology of cell membrane gangliosides. In: Ouchterlony Ö, Holmgren J, eds. *Cholera and Related Diarrheas. 43rd Nobel Symposium, Stockholm 1978.* New York, NY: S Karger AG; 1980:80-87.
15. Svennerholm L. Quantitative estimation of gangliosides in senile human brain. *Acta Societatis Medicorum Upsaliensis.* 1957;62:1-16.
16. Suzuki K. The pattern of mammalian brain gangliosides, III: regional and developmental differences. *J Neurochem.* 1965;12:969-979.
17. Ledeen RW, Skrivanek JA, Tirri LJ, Margolis RK, Margolis RU. Gangliosides of the neuron: localization and origin. *Adv Exp Med Biol.* 1976;71:83-103.
18. Wiegandt H. The subcellular localisation of gangliosides in the brain. *J Neurochem.* 1967;14:671-674.
19. Breckenridge WC, Gombos G, Morgan IG. The lipid composition of adult and rat brain synaptosomal plasma membranes. *Biochim Biophys Acta.* 1972;266:695-707.
20. Hansson HA, Holmgren J, Svennerholm L. Ultrastructural localization of cell membrane GM1 ganglioside by cholera toxin. *Proc Natl Acad Sci U S A.* 1977;74:3782-3786.
21. Doljanski F, Kapeller M. Cell surface shedding: the phenomenon and its possible significance. *J Theor Biol.* 1976;62:253-270.
22. Milhorat T, Hammock K. Cerebrospinal fluid as reflection of internal milieu of brain. In: Wood JH, ed. *Neurobiology of Cerebrospinal Fluid.* New York, NY: Plenum Press; 1983:1-23.
23. Davidsson P, Fredman P, Svennerholm L. Gangliosides and sulfatide in human cerebrospinal fluid: quantitation with immunoaffinity techniques. *J Chromatogr.* 1989;496:279-289.
24. Faber-Langendoen K, Morris JC, Knesewich JW, LaBerge E, Miller JP, Berg L. Aphasia in senile dementia of the Alzheimer type. *Ann Neurol.* 1988;23:365-370.
25. Folstein M, Folstein S, McHugh P. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.
26. Laurell CB. Electroimmunoassay. *Scand J Clin Lab Invest.* 1972;29:21-37.
27. Link H, Tibbling G. Principles of albumin and IgG analyses in neurological disorders, II: relation of the concentration of the proteins in serum and cerebrospinal fluid. *Scand J Clin Lab Invest.* 1977;37:391-396.
28. Davidsson P, Fredman P, Månsson JE, Svennerholm L. Determination of gangliosides and sulfatide in human cerebrospinal fluid with a microimmunoaffinity technique. *Clin Chim Acta.* 1991;197:105-116.
29. Holmgren J, Lönnroth I, Svennerholm L. Tissue receptor for cholera exotoxin: postulated structure from studies with G_{M1} ganglioside and related glycolipids. *Infect Immun.* 1973;8:208-214.
30. Lindholm L, Holmgren J, Wikström M, Karlsson U, Andersson K, Lycke N. Monoclonal antibodies to cholera toxin with special reference to cross-reactions to *Escherichia coli* heat labile enterotoxin. *Infect Immun.* 1983;40:570-576.
31. Ledeen RW, Yu RK. Gangliosides of CSF and plasma: their relation to the nervous system. In: Volk BW, Aronson SM, eds. *Sphingolipids, Sphingolipidoses and Allied Disorders.* New York, NY: Plenum Press; 1972:77-93.
32. Håkansson L, Fredman P, Svennerholm L. Gangliosides in serum immune complexes from tumor-bearing patients. *J Biochem.* 1985;98:843-849.
33. Lowden JA, Wolfe LS. Studies on brain gangliosides, III: evidence for the location of gangliosides specifically in neurons. *Can J Biochem.* 1964;42:1587-1594.
34. Ledeen R. Gangliosides of the neuron. *Trends Neurosci.* 1985;8:169-175.
35. Ledeen RW. Ganglioside structures and distribution: are they located at the nerve endings? *J Supramol Struct.* 1978;8:1-17.
36. Svennerholm L, Boström K, Fredman P, Månsson JE, Rosengren B, Rynmark BM. Human brain gangliosides: developmental changes from early fetal stage to advanced age. *Biochim Biophys Acta.* 1989;1005:109-117.
37. Tomlinson BE, Henderson G. Some quantitative cerebral findings in normal and demented old people. In: Terry RD, Gershon S, eds. *Neurobiology of Aging.* New York, NY: Raven Press; 1976:183-204.
38. Mountjoy CQ, Roth M, Evans NJR, Evans HM. Cortical neuronal counts in normal elderly controls and demented patients. *Neurobiol Aging.* 1983;4:1-11.
39. Hubbard BM, Anderson JM. Age-related variations in the neuron content of the cerebral cortex in senile dementia of Alzheimer type. *Neuropathol Appl Neurobiol.* 1985;11:369-382.



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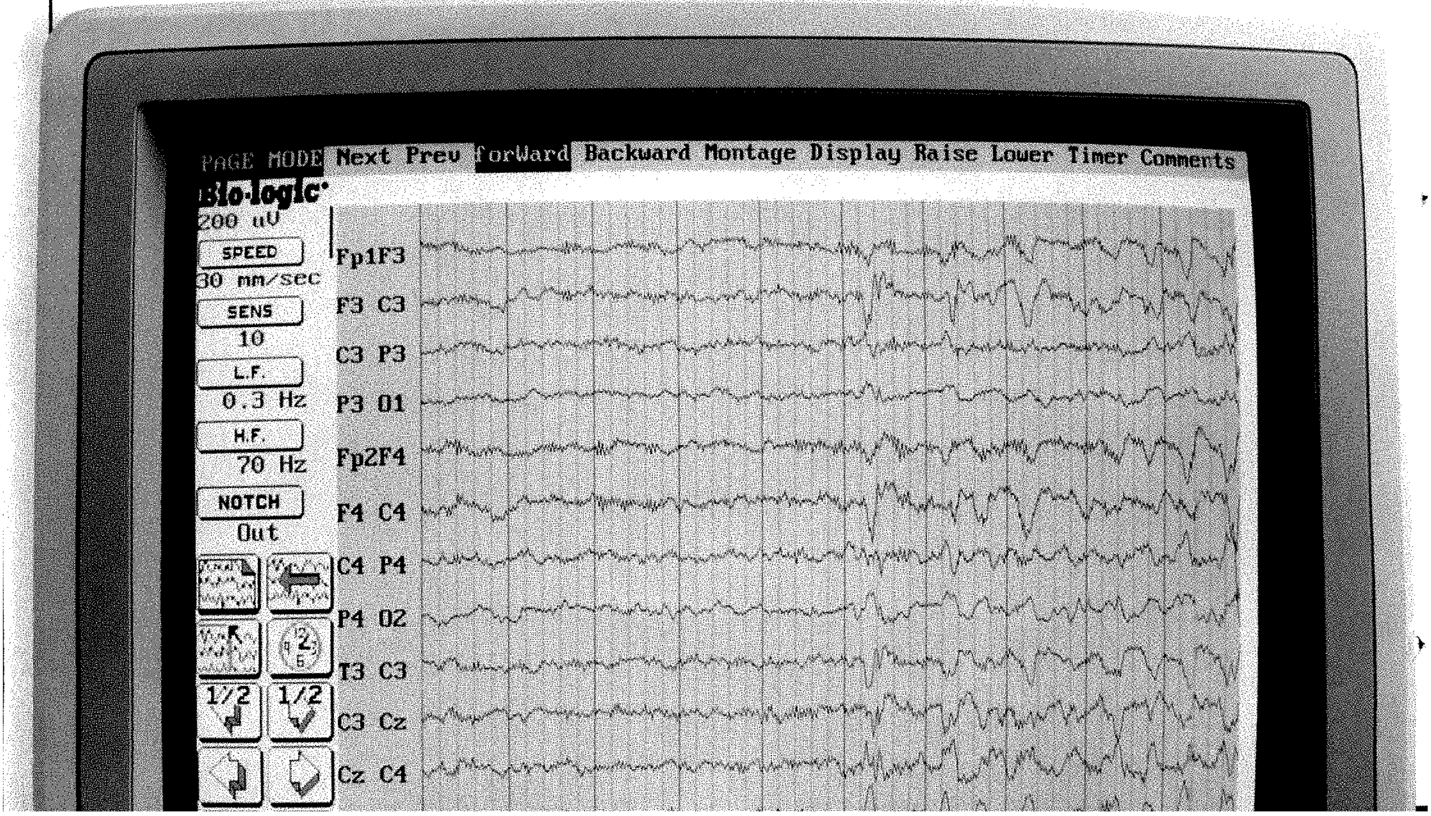

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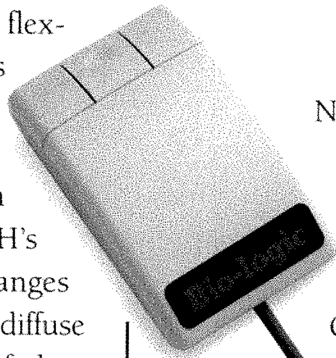

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Paired Associate Learning in Senile Dementia of the Alzheimer Type

Janet M. Duchek, PhD; Marshall Cheney, MA; F. Richard Ferraro, PhD; Martha Storandt, PhD

• A study was conducted to examine the potential explicit learning ability in senile dementia of the Alzheimer type (SDAT) as a function of (1) the difficulty of the to-be-remembered material and (2) the severity of the dementia. The Associate Learning task from the Wechsler Memory Scale was administered to healthy older adults and individuals with questionable, mild, and moderate SDAT. Individuals with SDAT showed poorer learning performance across trials than healthy older adults. Individuals with questionable and mild SDAT did show evidence for learning across trials for highly related paired associates. For unrelated-paired associates, however, only individuals with questionable SDAT showed some evidence for increased learning across trials.

(*Arch Neurol.* 1991;48:1038-1040)

Memory loss is a hallmark clinical symptom of the mild stages of senile dementia of the Alzheimer type (SDAT). Previous articles from the Washington University Memory and Aging Project have revealed a marked memory deficit associated with SDAT on a variety of psychometric measures.[1-3] Although it is clear that the overall memory performance of patients with SDAT is impaired compared with healthy older adults, it is not entirely clear whether patients with SDAT can demonstrate any learning across trials.

There is some evidence for learning in SDAT with implicit memory tasks in which the prior experience with the task facilitates performance without having to consciously recollect the prior experience. It has been reported that individuals with SDAT benefit as much as healthy older adults from the repeated exposure to items in a mirror reading task[4] and a semantic priming task.[5] People with SDAT also demonstrate implicit learning of motor tasks. For example, Knopman and Nissen[6] reported that patients with SDAT demonstrated learning of a repeated motor sequence across blocks of trials. Also, Heindel et al[7] found nearly identical learning curves for healthy older adults and patients with SDAT in a pursuit-rotor task.

The memory performance deficit associated with SDAT across many psychometric measures, however, involves explicit memory such as recall and recognition tasks. Individuals with SDAT exhibit large deficits in explicit memory tasks, but relatively little attention has been paid to explicit learning in SDAT. In the mild stages of the disease, individuals exhibit a typical U-shaped serial position curve.[8] That is, items from the beginning (ie, primacy) and end (ie, recency) of the list are better recalled than items from the middle of the list. It has been argued that the primacy effect reflects long-term memory processes, whereas the recency effect reflects short-term memory processes.[9] Thus, at least in the early stages of SDAT there is some evidence that material can be stored in a more durable long-term store. As the severity of the disease increases, however, the primacy effect diminishes followed finally by a loss of the recency effect.[8,10,11]

Other studies have examined the acquisition of new information by focusing on the learning curves of patients with SDAT across trials.[10,12] In both studies patients with SDAT exhibited a relatively flat learning curve. Little et al[13] reported that individuals with SDAT were able to retain paired associates over a 2-month interval, yet showed no evidence for increased retention across testing. Thus, unlike the implicit memory tasks, there appears to be little evidence for learning across trials in explicit memory tasks. It is possible, however, that individuals with SDAT can learn new information as a function of different task requirements.

The purpose of our study was to examine the potential explicit learning ability in SDAT as a function of (1) the difficulty of the to-be-remembered material and (2) the severity of the dementia. This was performed using the Associate Learning subtest from the Wechsler Memory Scale,[14] which involves the learning/retention of both easy and difficult paired associates across three trials. The task was administered to healthy control subjects and individuals with questionable, mild, and moderate SDAT. There have been previous articles of summary scores from this subtest with portions of the sample included herein.[1-3,15-17]

SUBJECTS AND METHODS

Participants in the patient registry of the Washington University Alzheimer's Disease Research Center, St Louis, Mo, were originally screened by physicians for depression,

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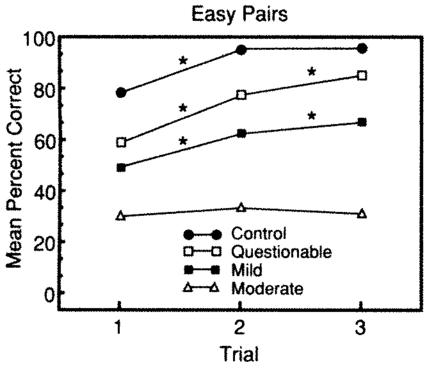

Fig 1.—Mean percent correct recall for easy pairs as a function of group and trial. Asterisk indicates a statistically significant increase between trials.

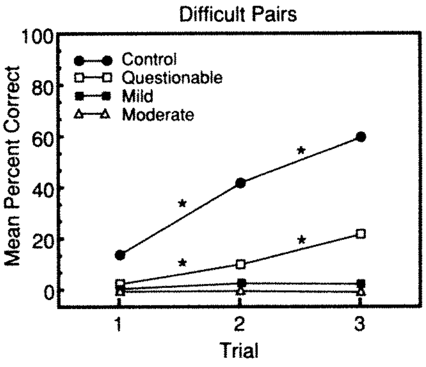

Fig 2.—Mean percent correct recall for difficult pairs as a function of group and trial. Asterisk indicates a statistically significant increase between trials.

severe hypertension, reversible dementias, or other disorders or medications that could potentially produce cognitive impairment.[18] The severity of the dementia was staged according to the Washington University Clinical Dementia Rating (CDR) scale where CDR 0, 0.5, 1, 2, and 3 represent no dementia, questionable, mild, moderate, and severe dementia, respectively.[19,20] The label "questionable dementia" (CDR 0.5) was initially used for individuals with very mild cognitive impairment such that the clinician was unsure whether the impairment would progress to SDAT until further longitudinal data had been collected. In fact, over time, the majority of these individuals clinically progressed to more severe stages of SDAT or Alzheimer's disease was verified post mortem. Thus, these results indicate that the CDR 0.5 represents a "very mild" stage of SDAT.[21-23]

In this analysis, there were 83 individuals who had a CDR of 0, 41 who had a CDR of 0.5, 66 who had a CDR of 1, and 21 who had a CDR of 2. Only data from the first time of testing were examined for those individuals enrolled for longitudinal study.

The diagnosis and staging of the disease is based on a 90-minute examination and interview with both the participant and a collateral source. The CDR is derived from the physicians' evaluation of the individual's cognitive abilities in the areas of memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. The reliability of the CDR and validity of the diagnosis have been reported elsewhere in the literature.[24-26]

The Wechsler Memory Scale[14] was administered as the first part of a 2-hour comprehensive psychometric battery that assesses various aspects of memory, psychomotor performance, and language.[2,3] The subtest measuring visual memory was omitted.

The Associate Learning subtest consists of a list of 10 paired associates. Six of the pairs are easy (ie, related) associates (eg, metal-iron) and four of the pairs are difficult (ie, unrelated) associates (eg, crush-dark). The 10 pairs are presented in a different order on each of three trials.

All participants were tested individually by a trained psychometrician. The test was administered and scored according to standard instructions. On the first trial, the list of 10 pairs was read to the participant. Following the presentation of the list, the psychometrician read the first word of each pair (eg, metal) and the participant was asked to respond with the word paired with the first word (eg, iron). The same procedure was followed on the second and third trials.

RESULTS

The percent correct recall for each person was calculated for easy and difficult pairs on each of the three trials. The easy and difficult pairs were analyzed separately. These data were analyzed using a 4 × 3-mixed factor analysis of variance. Group (healthy control, questionable dementia, mild dementia, moderate dementia) was the between-subject factor and trial (1, 2, or 3) was the within-subject factor.

The data from the easy pairs are presented in Fig 1 as a function of group and trial. There are four findings to note. First, the healthy control subjects overall showed better performance than all three SDAT groups. Second, the questionable SDAT group showed increasing performance across trials. Third, the mild SDAT group also showed increasing performance across trials 1 and 2 and a slight increase at trial 3. Fourth, the moderate SDAT group showed the same level of performance across all three trials.

These observations were supported by the following analyses. The overall analysis of variance indicated there was a significant main effect of group, F(3,207)=78.1, mean square error (MSe)=7.41, and trial, F(2,414)=71.19, MSe=1.31, and a group × trial interaction, F(6,414)=4.48, MSe=.08. Post hoc analyses indicated that the questionable SDAT group showed a significant increase in performance from trial 1 to trial 2, F(1,40)=34.23, MSe=.81; and trial 2 to trial 3, F(1,40)=8.35, MSe=.12. The mild SDAT group also showed a significant increase in performance from trial 1 to trial 2, F(1,65)=30.74, MSe=.66; and a slight increase from trial 2 to trial 3, F(1,65)=4.14, MSe=.07, *P*=.05, although the slope of the learning curve was greater for the questionable (13.8) than the mild SDAT group (9.35).

The data from the difficult pairs are presented in Fig 2. There are three findings to note. First, the healthy control subjects showed better performance across trials than all three SDAT groups. Second, the questionable SDAT group showed increasing performance across trials. Third, both the mild and moderate SDAT groups' performance represents a floor effect.

These observations were supported by the following analyses. The overall analysis of variance indicated there was a significant main effect of group, F(3,207)=73.59, MSe=6.62, and trial, F(2,414)=66.00, MSe=1.34, and a group × trial interaction, F(6,414)=37.97, Mse=.77. Post hoc analyses indicated that the questionable SDAT group showed a significant increase in performance from trial 1 to trial 2, F(1,40)=12.56, MSe=.15; and trial 2 to trial 3, F(1,40)=14.87, MSe=.30.

COMMENT

The purpose of this study was to examine the explicit learning ability in SDAT as a function of (1) the difficulty of the to-be-remembered material and (2) the severity of the dementia. The results are straightforward with respect to both issues.

It is clear that SDAT individuals show poorer learning performance across trials than healthy older adults even when the to-be-remembered material is relatively easy. However, despite the overall lower level of performance, individuals with questionable and mild SDAT did show evidence for increased learning across trials for the easy (ie, highly related) paired associates. On the other hand, individuals in the moderate stage of SDAT showed a relatively flat learning curve across trials for the easy material. Finally, for the difficult pairs, only nondemented individuals or those with questionable SDAT showed some evidence for increased learning across trials. Both the mildly and moderately demented individuals were virtually unable to learn any of the difficult pairs across trials.

This study provides evidence that individuals in the milder stages of SDAT can benefit from the repetition of material across trials in an explicit memory task. As previously mentioned, there is literature supporting learning across trials in SDAT for implicit memory tasks.[4,6,7] There is, however, little evidence for learning in explicit memory tasks, such as recall or recognition, which require the conscious retrieval of information from memory. Bigler et al[10] reported a relatively flat learning curve for early-stage DAT patients across five trials, although performance did increase slightly from the first trial (March 15) to the last trial (May 15). One possible explanation for the failure to demonstrate learning in Bigler and coworkers' study may be due to the type of task used. Learning was assessed with the Rey-Auditory Verbal Learning Test,[27] which involves the free recall of a 15-item list. It has been argued that free recall is a more cognitively demanding task than a cued recall task such as a paired associate task.[28] Thus, it is possible that individuals with SDAT may not show evidence of learning in more cognitively demanding tasks.

Our study provides support that individuals with SDAT can acquire new information that is relatively easy with a less cognitively demanding task, such as cued recall. As previously noted, El-Awar et al[12] used a paired associate task and still found no evidence for learning across 10 trials in patients with SDAT. The list, however, contained 10 unrelated paired associates, which would be similar to the difficult pairs in this study. Thus, the results of El-Awar and coworkers' study are similar to our finding that mildly or moderately demented individuals do not show evidence for learning difficult material across trials.

In conclusion, individuals in the milder stages of SDAT do show evidence for explicit learning ability when the to-be-remembered information is "easy" (ie, makes use of well-established associations in memory). On the other hand, if the to-be-remembered material is more difficult in nature (ie, does not make use of existing associations), individuals even in the least severe stages of Alzheimer's disease show little evidence for learning.

Craik et al[28] argued that the magnitude of the memory deficit associated with normal aging depends on the type of task and materials used, as well as characteristics of the subject population. The more the task and materials support the cognitive processing (eg, a cued recall task), the smaller the age-related memory deficit. One could make a similar argument regarding the learning ability of individuals with SDAT. People with SDAT can learn new information when (1) the disease is not severe, (2) the cognitive demands of the task are minimized, and (3) the to-be-remembered information makes use of existing associations in the memory network. As the disease progresses, however, there is little evidence for learning even when the task and materials support the cognitive processing.

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References

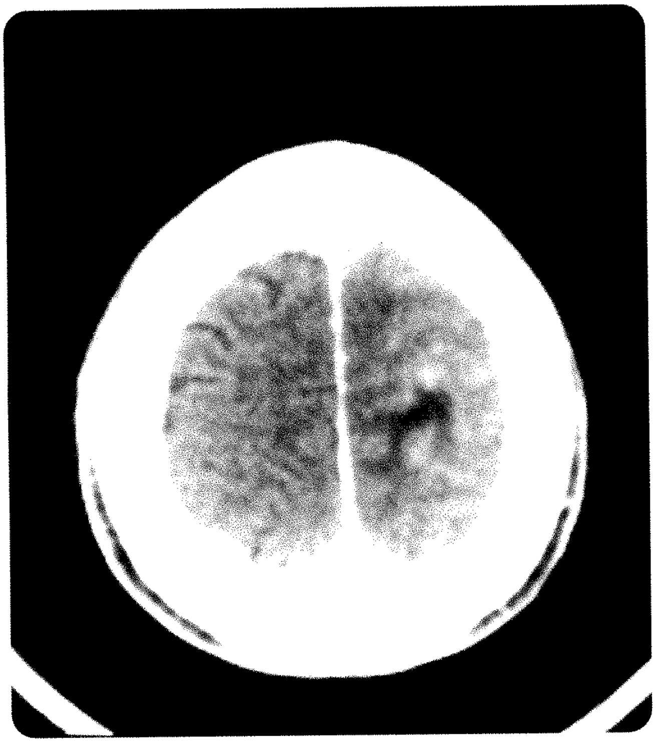
1. Botwinick J, Storandt M, Berg L. A longitudinal, behavioral study of senile dementia of the Alzheimer type. *Arch Neurol.* 1986;43:1124-1127.
2. Storandt M, Botwinick J, Danziger WL, Berg L, Hughes CP. Psychometric differentiation of mild senile dementia of the Alzheimer type. *Arch Neurol.* 1984;41:497-499.
3. Storandt M, Hill R. Very mild dementia of the Alzheimer type, II: psychometric test performance. *Arch Neurol.* 1986;46:383-386.
4. Moscovitch M, Winocur G, McLachlan D. Memory as assessed by recognition and reading time in normal and memory-impaired people with Alzheimer's disease and other neurological disorders. *J Exp Psychol [Gen].* 1986;115:331-347.
5. Balota DA, Duchek JM. Semantic priming effects, lexical repetition effects, and contextual disambiguation effects in healthy aged individuals and individuals with senile dementia of the Alzheimer type. *Brain Lang.* 1991;40:181-201.
6. Knopman DS, Nissen MJ. Implicit learning in patients with probable Alzheimer's disease. *Neurology.* 1987;37:784-788.
7. Heindel WC, Salmon DP, Shults CW, Walicke PA, Butters N. Neuropsychological evidence for multiple implicit memory systems: a comparison of Alzheimer's, Huntington's, and Parkinson's disease patients. *J Neurosci.* 1989;9:582-587.
8. Pepin EP, Eslinger PJ. Verbal memory decline in Alzheimer's disease: a multiple-processes deficit. *Neurology.* 1989;39:1477-1482.
9. Crowder RG. *Principles of Learning and Memory.* Hillsdale, NJ: Lawrence Erlbaum Associates; 1976.
10. Bigler ED, Rosa L, Schultz F, Hall S, Harris J. Rey-auditory verbal learning and Rey-Osterrieth complex figure design performance in Alzheimer's disease and closed head injury. *J Clin Psychol.* 1989;45:277-280.
11. Harris SJ, Dowson JH. Recall of a 10-word list in the assessment of dementia in the elderly. *Br J Psychiatry.* 1982;141:524-527.
12. El-Awar M, Becker JT, Hammond KM, Nebes RD, Boller F. Learning deficit in Parkinson's disease: comparison with Alzheimer's disease and normal aging. *Arch Neurol.* 1984;44:180-184.
13. Little AG, Volans PJ, Hemsley DR, Levy R. The retention of new information in senile dementia. *Br J Clin Psychol.* 1986;25:71-72.
14. Wechsler D, Stone CP. *Manual: Wechsler Memory Scale.* New York, NY: Psychological Corp; 1973.
15. Botwinick J, Storandt M, Berg L, Boland S. Subject attrition and testability in research on senile dementia of the Alzheimer type. *Arch Neurol.* 1988;45:493-496.
16. Storandt M. Longitudinal studies of aging and age-associated dementia. In: Corkin S, ed. *Handbook of Neuropsychology.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1990.
17. Storandt M, Botwinick J, Danziger WL. Longitudinal changes, mild SDAT and matched healthy controls. In: Poon LW, ed. *Handbook for the Clinical Memory Assessment of Older Adults.* Washington, DC: American Psychological Association; 1986.
18. Berg L, Hughes CP, Coben LA, Danziger WL, Martin RL, Knesevich J. Mild senile dementia of the Alzheimer type (SDAT): research diagnostic criteria, recruitment, and description of a study population. *J Neurol Neurosurg Psychiatry.* 1982;45:962-968.
19. Berg L. Clinical dementia rating (CDR). *Psychopharm Bull.* 1988;24:637-639.
20. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140:566-572.
21. Morris JC, McKeel DW Jr, Price JL, et al. Very mild senile dementia of the Alzheimer type (SDAT). *Neurology.* 1988;38(suppl 1):227. Abstract.
22. Rubin EH, Morris JC, Grant EA, Vendegna T. Very mild senile dementia of the Alzheimer type, I: clinical assessment. *Arch Neurol.* 1989;46:379-382.
23. Storandt M, Hill R. Very mild senile dementia of the Alzheimer type, II: psychometric test performance. *Arch Neurol.* 1989;46:383-386.
24. Berg L, Smith DS, Morris JC, et al. Mild senile dementia of the Alzheimer type, III: longitudinal and cross-sectional assessment. *Ann Neurol.* 1990;28:648-652.
25. Burke WJ, Miller JP, Rubin EG, et al. Reliability of the Washington University clinical dementia rating. *Arch Neurol.* 1988;45:31-32.
26. Morris JC, McKeel DW Jr, Fulling K, Torack RM, Berg L. Validation of clinical diagnostic criteria for Alzheimer's disease. *Ann Neurol.* 1988;24:17-22.
27. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol.* 1941;28:286-340.
28. Craik FIM, Byrd M, Swanson JM. Patterns of memory loss in three elderly samples. *Psychol Aging.* 1987;2:79-86.

THE DECISION IS YOURS.

COMPARE.

THE CASE: A 40-year-old man presented with a 2-month history of involuntary muscle contractions of the right arm and mild weakness of the left leg.

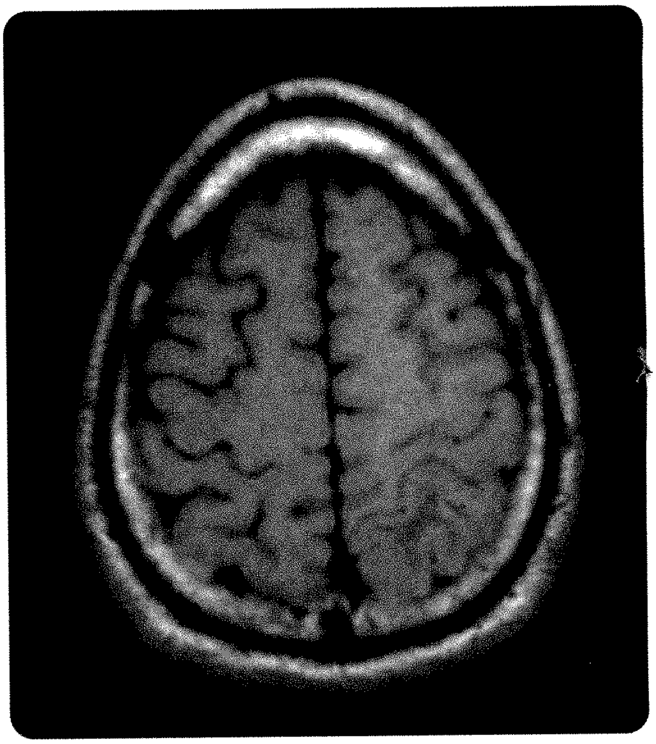
First there was CT.



Contrast CT scan shows an area of low attenuation in the left parietal lobe. A questionable focus of contrast is seen, but this may represent cerebral cortex.

Images courtesy of Michael R. Ross, MD, Stanford University Medical Center, Stanford, California

Then MRI.



T1-weighted (TR 800/TE 20) unenhanced MR image, obtained with a 1.5-T imager, shows subcortical hypointensity in the left posterior parietal lobe. The surrounding sulci appear to be compressed, but a mass is not clearly appreciated.

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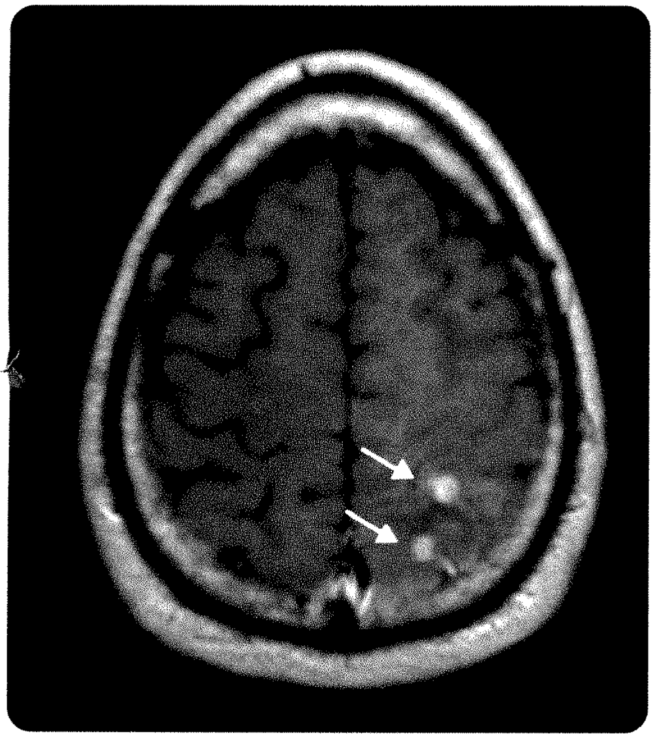
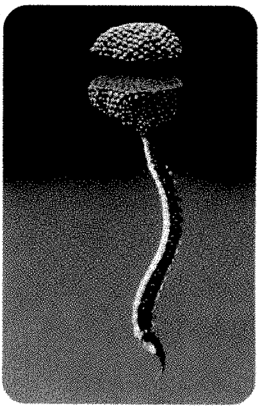
AND CONTRAST.

Now, *Magnevist*®-enhanced MRI lets you see even more.



T1-weighted (TR 800/TE 20) image enhanced with MAGNEVIST® injection reveals two discrete nodules (arrows). This nodular enhancement is highly suggestive of a primary brain tumor, which was confirmed upon biopsy to be an astrocytoma.



Magnevist®

(gadopentetate dimeglumine 469.01 mg/mL)

INJECTION

NOTHING LOCATES LESIONS BETTER

Please see brief summary of prescribing information for MAGNEVIST® injection on last page of this advertisement.

Well tolerated[1] In clinical trials, the most common adverse reactions reported were headache (8.7%) and injection-site coldness/localized coldness (4.8%). The majority of headaches were transient and of mild to moderate severity. In clinical trials, 15% to 30% of patients experienced an asymptomatic transient rise in serum iron; hypotension and anaphylactoid reactions have occurred in less than 1% of the patients. The safety of MAGNEVIST® injection in patients with hemolytic disorders has not been studied.

REFERENCE: 1. Data on file, Berlex Laboratories, Inc.

BRIEF SUMMARY

INDICATIONS AND USAGE

MAGNEVIST® Injection is indicated for use with magnetic resonance imaging (MRI) in adults and children (2 years of age and older) to provide contrast enhancement in those intracranial lesions with abnormal vascularity or those thought to cause an abnormality in the blood-brain barrier. MAGNEVIST® Injection has been shown to facilitate visualization of intracranial lesions including but not limited to tumors.

MAGNEVIST® Injection is also indicated for use with MRI in adults and children (2 years of age and older) to provide contrast enhancement and facilitate visualization of lesions in the spine and associated tissues. There is, however, only limited clinical experience in children for this indication.

CONTRAINDICATIONS

None known.

WARNINGS

The accepted safety considerations and procedures that are required for magnetic resonance imaging are applicable when MAGNEVIST® Injection is used for contrast enhancement. In addition, deoxygenated sickle erythrocytes have been shown in *in vitro* studies to align perpendicular to a magnetic field which may result in vaso-occlusive complications *in vivo*. The enhancement of magnetic moment by gadopentetate dimeglumine may possibly potentiate sickle erythrocyte alignment. MAGNEVIST® Injection in patients with sickle cell anemia and other hemoglobinopathies has not been studied.

Patients with other hemolytic anemias have not been adequately evaluated following administration of MAGNEVIST® Injection to exclude the possibility of increased hemolysis.

Hypotension may occur in some patients after injection of MAGNEVIST® Injection. In clinical trials two cases were reported and in addition, there was one case of a vasovagal reaction and two cases of pallor with dizziness, sweating and nausea in one and substernal pain and flushing in the other. These were reported within 25 to 85 minutes after injection except for the vasovagal reaction which was described as mild by the patient and occurred after 6-1/2 hours. In a study in normal volunteers one subject experienced syncope after arising from a sitting position two hours after administration of the drug. Although the relationship of gadopentetate dimeglumine to these events is uncertain, patients should be observed for several hours after drug administration.

Magnevist®
(gadopentetate dimeglumine 469.01 mg/mL)
INJECTION

PRECAUTIONS - General

Diagnostic procedures that involve the use of contrast agents should be carried out under direction of a physician with the prerequisite training and a thorough knowledge of the procedure to be performed.

In a patient with a history of grand mal seizures, MAGNEVIST® Injection was reported to induce such a seizure.

Since gadopentetate dimeglumine is cleared from the body by glomerular filtration, caution should be exercised in patients with severely impaired renal function.

The possibility of a reaction, including serious, life-threatening, fatal, anaphylactoid or cardiovascular reactions or other idiosyncratic reactions should always be considered (see ADVERSE REACTIONS) especially in those patients with a known clinical hypersensitivity.

Animal studies suggest that gadopentetate dimeglumine may alter red cell membrane morphology resulting in a slight degree of extravascular (splenic) hemolysis. In clinical trials 15-30% of the patients experienced an asymptomatic transient rise in serum iron. Serum bilirubin levels were slightly elevated in approximately 3.4% of patients. Levels generally returned to baseline within 24 to 48 hours. Hematocrit and red blood cell count were unaffected and liver enzymes were not elevated in these patients. While the effects of gadopentetate dimeglumine on serum iron and bilirubin have not been associated with clinical manifestations, the effect of the drug in patients with hepatic disease is not known and caution is therefore advised.

When MAGNEVIST® Injection is to be injected using plastic disposable syringes, the contrast medium should be drawn into the syringe and used immediately.

If nondisposable equipment is used, scrupulous care should be taken to prevent residual contamination with traces of cleansing agents.

Repeat Procedures: If in the clinical judgment of the physician sequential or repeat examinations are required, a suitable interval of time between administrations should be observed to allow for normal clearance of the drug from the body.

Information for Patients:

Patients receiving MAGNEVIST® Injection should be instructed to:

1. Inform your physician if you are pregnant or breast feeding.
2. Inform your physician if you have anemia or any diseases that affect red blood cells.

LABORATORY TEST FINDINGS

Transitory changes in serum iron and bilirubin levels have been reported in patients with normal and abnormal liver function (See PRECAUTIONS - General).

CARCINOGENESIS, MUTAGENESIS, AND IMPAIRMENT OF FERTILITY

No animal studies have been performed to evaluate the carcinogenic potential of gadopentetate dimeglumine.

Gadopentetate dimeglumine did not evoke any evidence of mutagenic potential in the Ames test (histidine-dependent *Salmonella typhimurium*) nor in a reverse mutation assay using tryptophan-dependent *Escherichia coli*. Gadopentetate dimeglumine did not induce a positive response in the (C3H 10T1/2) mouse embryo fibroblast cellular transformation assay, nor did it induce unscheduled DNA repair synthesis in primary cultures of rat hepatocytes at concentrations up to 5000 μg/mL. However, the drug did show some evidence of mutagenic potential *in vivo* in the mouse dominant lethal assay at doses of 6 mmol/kg, but did not show any such potential in the mouse and dog micronucleus tests at intravenous doses of 9 mmol/kg and 2.5 mmol/kg, respectively.

The results of a reproductive study in rats showed that gadopentetate dimeglumine when administered in daily doses of 0.1-2.5 mmol/kg, did not cause a significant change in the pregnancy rate in comparison to a control group. However, suppression of body weight gain and food consumption and a decrease in the mean weights of testis and epididymis occurred in male rats at the 2.5 mmol/kg dose. In female rats a decrease in the number of corpora lutea at the 0.1 mmol/kg dose and the suppression of body weight gain and food consumption at the 2.5 mmol/kg dose were observed.

In a separate experiment, 16 daily intravenous injections were administered to male rats. At a dose of 5 mmol/kg of gadopentetate dimeglumine, spermatogenic cell atrophy was observed. This atrophy was not reversed within a 16-day observation period following the discontinuation of the drug. This effect was not observed at a dose of 2.5 mmol/kg.

PREGNANCY CATEGORY C.

Gadopentetate dimeglumine has been shown to retard development slightly in rats when given in doses 2.5 times the human dose, and in rabbits when given in doses of 7.5 and 12.5 times the human dose. The drug did not exhibit this effect in rabbits when given in doses 2.5 times the human dose. No congenital anomalies were noted in either species.

There are no adequate and well-controlled studies in pregnant women. MAGNEVIST® Injection should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

NURSING MOTHERS

C^{14} labelled gadopentetate dimeglumine was administered intravenously to lactating rats at a dose of 0.5 mmol/kg. Less than 0.2% of the total dose was transferred to the neonate via the milk during the 24-hour evaluation period. It is not known to what extent MAGNEVIST® Injection is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when the drug is administered to a nursing mother and consideration should be given to temporarily discontinuing nursing.

PEDIATRIC USE

Safety and efficacy in children under the age of 2 years have not been established. (See Indications and Usage and Dosage and Administration sections).

ADVERSE REACTIONS

The most commonly noted adverse experience is headache with an incidence of 8.7%. The majority of headaches are transient and of mild to moderate severity. In 42.3% of the cases it was felt that the headaches were not related to MAGNEVIST® Injection. Injection site coldness/localized coldness is the second most common adverse experience at 4.8%. Nausea occurs in 3.2% of the patients.

Localized pain, vomiting, paresthesia, dizziness and localized warmth occur in less than 2% of the patients.

The following additional adverse events occur in less than 1% of the patients:

Body as a Whole: Injection site symptoms, namely, pain, warmth, burning; localized burning sensation, substernal chest pain, fever, weakness, generalized coldness, localized edema, tiredness, chest tightness, regional lymphangitis, anaphylactoid reactions (characterized by cardiovascular, respiratory and cutaneous symptoms).

Cardiovascular: Hypotension, vasodilation, pallor, non-specific ECG changes, angina pectoris, phlebitis.

Digestive: Gastrointestinal distress, stomach pain, teeth pain, increased salivation.

Nervous System: Agitation, thirst, convulsions (including grand mal).

Respiratory System: Throat irritation, rhinorrhea, sneezing, dyspnea, wheezing, laryngismus, cough.

Skin: Rash, sweating, pruritus, urticaria (hives).

Special Senses: Tinnitus, conjunctivitis, visual field defect, taste abnormality, dry mouth, lacrimation disorder (tearing), eye irritation.

Laboratory: Transient elevation of serum transaminases.

The following other adverse events were reported. A causal relationship has neither been established nor refuted.

Body as a Whole: Back pain, pain, generalized warmth.

Cardiovascular: Hypertension, tachycardia, migraine, syncope, death related to myocardial infarction or other undetermined causes.

Digestive: Constipation, diarrhea.

Nervous System: Anxiety, anorexia, nystagmus, drowsiness, diplopia, stupor.

Skin: Facial edema, erythema multiforme, epidermal necrolysis.

Special Senses: Eye pain, ear pain.

Data from foreign studies did not reveal any additional adverse experiences.

OVERDOSAGE

The LD_{50} of intravenously administered gadopentetate dimeglumine injection in mice is 5-12.5 mmol/kg and in rats it is 10-15 mmol/kg. The LD_{50} of intravenously administered MAGNEVIST® Injection in dogs is greater than 6 mmol/kg.

Clinical consequences of overdose with MAGNEVIST® Injection have not been reported.

DOSAGE AND ADMINISTRATION

The recommended dosage of MAGNEVIST® Injection is 0.2 mL/kg (0.1 mmol/kg), administered intravenously, at a rate not to exceed 10 mL per minute. More rapid injection rates may be associated with nausea. The maximum total dose is 20 mL. Any unused portion must be discarded.

DOSAGE CHART

Body Weight (kg)	Dose in mL	Approx Duration of Injection in Seconds
10	2.0	20
20	4.0	30
30	6.0	40
40	8.0	50
50	10.0	60
60	12.0	70
70	14.0	80
80	16.0	95
90	18.0	110
100	20.0	120

To ensure complete injection of the contrast medium, the injection should be followed by a 5-mL normal saline flush. The imaging procedure should be completed within 1 hour of injection of MAGNEVIST® Injection.

Parenteral products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

For full prescribing information, see package insert.

Caution: Federal Law Prohibits Dispensing Without Prescription.

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IMAGING®

Monozygotic Twins With Seizures

Shared Characteristics

Rosalind A. Segal, MD, PhD; Catherine Chapman, MD; John Barlow, MD†

• Eleven sets of monozygotic twins with idiopathic seizure disorders seen at Children's Hospital, Boston, Mass, were reviewed. Nine twin pairs were concordant for seizures. A marked correlation in the precise timing of onset of seizures was found; three sets of twins had their first clinical seizures within a 24-hour period of one another. The clinical features of the seizures and the electroencephalographic patterns, including the location of focal discharges, were strikingly similar in the twin pairs. The significance of these findings in suggesting aberrant processes that may contribute to epileptic syndromes is discussed.

(*Arch Neurol.* 1991;48:1041-1045)

Monozygotic twins with epilepsy provide an opportunity to delineate the genetically determined features of a seizure disorder. Lennox[1] and others[2-4] have previously shown that there is a high degree of concordance in the incidence of epilepsy in monozygotic twins; this suggests that genetic factors are often responsible for an idiopathic seizure disorder. The characteristics of epilepsy that are inherited can also be delineated by investigating monozygotic twins.

The electroencephalographic (EEG) patterns of twins have been compared; the striking similarities seen in monozygotic twins with primary generalized seizures imply that certain characteristic patterns are inherited. Gedda and Tatarelli[2] and Vercelleto and Courjon[4] have noted the frequent correlation in the time of onset of clinical seizures in sets of monozygotic twins. In this article, we present 11 sets of monozygotic twins with idiopathic seizure disorders of varying severity. The concordance of the clinical seizure manifestations, the EEG patterns, and, most strikingly, the timing of onset of the first clinical seizure implicate genetic determinants in these characteristics for both focal and generalized idiopathic epilepsy.

PATIENTS AND METHODS

Members of the Department of Neurology at Children's Hospital, Boston, Mass, were asked to submit names of monozygotic twins, one or both of whom had been seen in the previous 15 years for idiopathic seizures. Any patients with seizures due to tumor, hemorrhage, known trauma, or with febrile seizures only were excluded from this study. All patients had been evaluated at Children's Hospital by a staff neurologist. The charts, and, when possible, the EEGs and imaging studies were reviewed by us. Monozygosity was assessed based on the clinical appearance of the twins. The EEGs were performed and reviewed for asymptomatic twins without charge specifically for this study.

RESULTS

Eleven sets of monozygotic twins seen at Children's Hospital between 1974 and 1989 were evaluated. All these represent children with idiopathic epilepsy. The data are summarized in Tables 1 and 2. As shown in Table 1, nine (82%) of the twins were concordant for seizures. Most impressively, the time of onset of seizure disorders was similar in the twins. Three sets of twins (30%) had their first seizure within 24 hours of one another (pairs 1, 2, and 3). Details of these three instances of synchronous onset are provided below. A fourth family, consisting of a set of triplets, two monozygotic twins with epilepsy of near synchronous onset, and a dizygotic triplet with no seizure history, is also described in further detail below. The concordance in time of onset of seizure disorders is further emphasized by the fact that the mean interval between the onset of seizures in cotwins was less than 3 months in the eight cases that can be analyzed (the twins discordant for seizures, pairs 7 and 10 and pair 5, where age of onset was not known, are excluded from this calculation).

The clinical characteristics and the EEG patterns of the twins were also similar, both for primary generalized and for partial seizures (Table 2). Both pairs of twins with partial seizures had the same location of focal discharges (pairs 1 and 2). The medication regimens that adequately controlled seizures in the twins were compared as shown in Table 2; in six cases the twins were treated with the same medications. In the two pairs with myoclonic seizures, the cotwins were receiving different anticonvulsants.

Pair 1

These male monozygotic twins were born at 36 weeks' gestation to nonconsanguineous parents of Italian descent. Twin B presented at the age of 8 months, after a seizure in which his eyes deviated to the left, and his left arm extended upward. The following day, twin A had a seizure that was identical in appearance. The twins were afebrile. Both twins were microcephalic and had severe developmental delay. The EEGs of both individuals showed hypsarrhythmia; thus, each twin fulfilled the three criteria for West syndrome.[5]

Accepted for publication May 17, 1991.

From the Department of Neurology, Children's Hospital, Boston, Mass.

† Deceased.

Reprint requests to the Department of Neurology, Children's Hospital, 300 Longwood Ave, Boston, MA 02115 (Dr Segal).

Computed tomographic scan of the head and magnetic resonance imaging showed mild ventricular dilatation and poor gray-white differentiation.

Both patients were initially treated with adrenocorticotropic hormone and valproate. There was subsequent improvement in clinical seizure incidence, in developmental progression, and in their EEGs. As adrenocorticotropic hormone was tapered, both twins showed a dramatic increase in seizure frequency. The EEGs at that time (age 13 months) showed evidence of a right-sided temporal focus in both twin A and twin B (Fig 1). They were treated with carbamazepine in addition to valproate, with a subsequent clear reduction in seizure frequency. A detailed investigation into a possible metabolic or prenatal infectious explanation for the patients' clinical condition did not reveal any specific cause.

Table 1.—Seizure Onset

Twin Pair	Age of First Seizure	Time Interval Between Cotwins' First Seizures
1	8 mo	<24 h
2	6 y	<24 h
3	3.5 mo	4 h
4	5 y	10 d
5	<1 y	Unknown
6	15 mo; 23 mo	8 mo
7	9 y	Second twin seizure free
8	6 mo; 7 mo	17 d
9	10 y; 11 y	8 mo
10	15 mo	Second twin seizure free
11	9 mo; 10 mo	1 mo

Pair 2

Twins A and B were left- and right-handed 6-year-old girls, respectively, referred to the neurology clinic for evaluation of their seizure disorders. They were born after a full-term uncomplicated pregnancy, delivered to a 23-year-old gravida 1, para 0-2 healthy woman by elective cesarean section. Twin A weighed 2664 g (5 lb/14 oz) and twin B weighed 2920 g (6 lb/7 oz). Both twins had a normal perinatal course, and normal subsequent growth and development. At 6 years of age, twin A fell and began crying. Her mother stated she then became limp, her eyes rolled up, and she had clonic movements of the upper and lower extremities lasting a few minutes. She was brought to a nearby hospital. While the parents were registering, twin B began to sway, then collapsed to the floor, lost consciousness, and had clonic movements of all extremities. The patients were afebrile, and laboratory evaluations, including complete blood cell count and toxic screen, were normal. The EEGs performed the following day revealed left-sided temporal discharges in both girls. Neurologic examination was normal. The girls were subsequently unavailable for follow-up, and so the results of imaging studies and their further clinical course are not known.

Pair 3

These patients were monozygotic twin girls, the 38-week gestation products of an uncomplicated pregnancy to a gravida 2 mother. They were delivered by cesarean section, and had a normal perinatal course. At 3.5 months of age, twin A had a generalized tonic-clonic seizure. A second seizure, 2.5 hours later, was also generalized tonic-clonic activity, with a possible right-side focal onset. Four and a half hours after twin A's first episode, while twin A was being evaluated in the emergency department, twin B had a generalized tonic-clonic seizure. Twin B had a second generalized seizure shortly thereafter. Neither patient was febrile nor was there any evidence of intercurrent illness. Evaluation revealed normal electrolyte concentrations, blood cell count, calcium level, and renal function. The cerebrospinal fluid glucose level, protein concentration, and cell count were all normal. However, both twins had markedly elevated serum alkaline phosphatase levels (3577 and 2400 mU/mL, respectively). The combination of seizures and elevated alkaline phosphatemia suggested the possibility that these girls had a variant of Mabry's syndrome,[6] which has been reported as a familial syndrome of hyperphosphatasia, seizures, and mental retardation. Unlike the family reported by Mabry et al, the twins were intellectually normal. Electroencephalograms and computed

Table 2.—Seizure Characteristics*

Twins	Clinical Seizure Type	EEG	Response to Anticonvulsants
1	Myoclonic/atypical absence	At 8 mo, generalized burst suppression; at 13 mo, right temporal focus	ACTH-I, Valproic acid-IV, Carbamazepine-III
2	Complex partial with secondary generalization	Left temporal discharges	Unknown
3	Generalized tonic-clonic	Both normal	Phenobarbital-I
4	Generalized tonic-clonic and atypical absence	Frequent bursts of irregular spike and wave	Valproic acid-I
5	Myoclonic	Photoparoxysmal response to strobe	Clonazepam-I for twin A; Valproic acid-I for twin B
6	Myoclonic	Multifocal polyspike and wave with photoparoxysmal response to strobe	Clonazepam-I, twin A; Clonazepam + Phenobarbital-I, twin B
7	Tonic—twin A only	Twin A, normal (age 9 y); twin B, bursts of generalized spike and wave (age 9 y)	No treatment
8	Twin B—partial with secondary generalization; twin A—generalized tonic-clonic	Bursts of spike and slow wave	Phenobarbital + Diphenylhydantoin-III
9	Generalized tonic-clonic	Generalized spike and wave with photoparoxysmal response to strobe	Diphenylhydantoin-I
10	Generalized tonic-clonic twin B only	Both normal (twin B at 15 mo, twin A at 3 y)	Phenobarbital-I, twin B; twin A not treated
11	Generalized tonic-clonic	Both normal	Mephobarbital + carbamazepine-I, twin A; II, twin B

*EEG indicates electroencephalogram; I, seizure free with or without aura for 1 year or more; II, no more than one seizure per year; III, worthwhile reduction in seizures (greater than or equal to 90% improved); IV, no worthwhile reduction in seizures; and ACTH, adrenocorticotropic hormone.

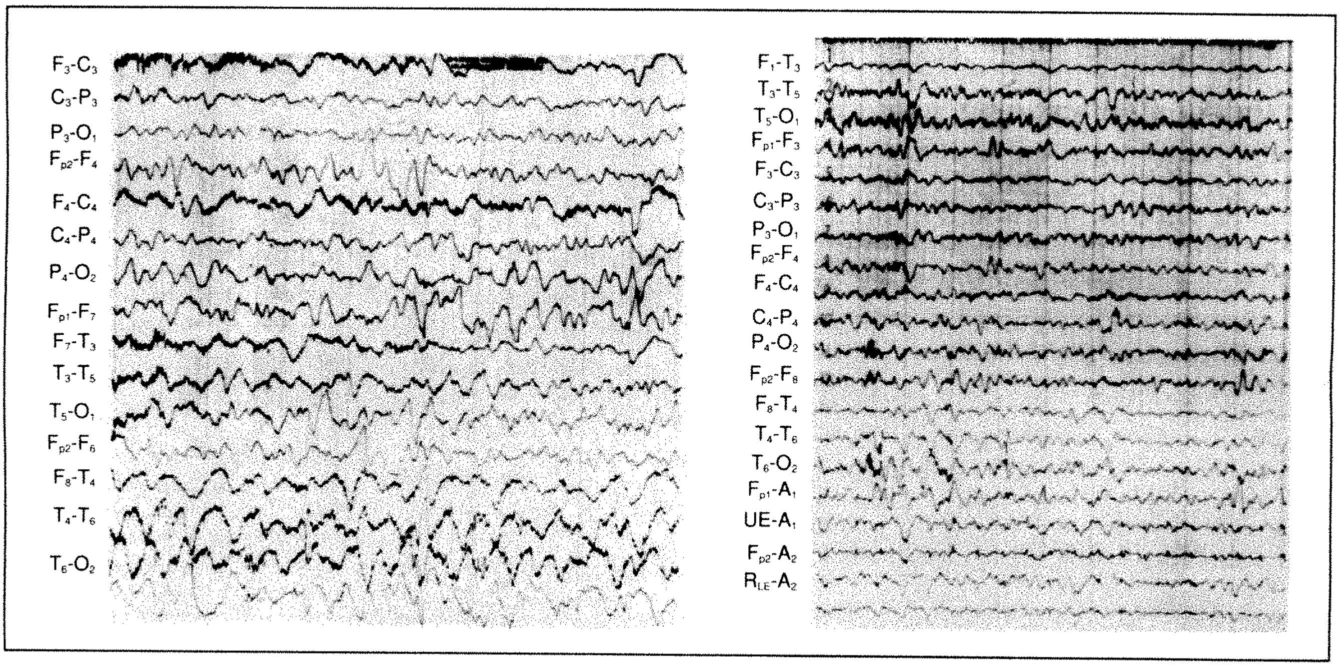


Fig 1.—Portions of electroencephalograms from pair 1. Twin A (left) and twin B (right) at 16 months of age. Both children were receiving valproate alone at the time of these electroencephalograms. A right temporal spike-wave complex with phase reversal over T_6 is demonstrated in both cases.

tomographic scans of the head were normal in both twins. The patients were treated with phenobarbital for the next year, during which time they had no subsequent seizures.

Set 4

These children were products of a 31-week, triple-gestation pregnancy, born to a 30-year-old gravida 1 mother. The triplets consisted of monozygotic twin girls, weighing 1502 (3 lb/5 oz) (twin A), and 1445 g (3 lb/3 oz) (twin B), and a dizygotic triplet boy, weighing 1247 g (2 lb/12 oz). Their neonatal course was notable for the fact that twin B had an aspiration pneumonia at 3 weeks of age. Subsequently, the growth and development of the triplets was within normal limits.

When twin B was 5 years old, she was found on the floor unresponsive, and incontinent of urine. An EEG showed generalized spike and wave activity; ethosuximide was prescribed (Fig 2). Ten days later, twin A was discovered by her sister, lying on the floor with her eyes rolled back, and making pursing movements of her lips. This episode lasted 2 minutes. An EEG also showed bursts of generalized spike and wave activity (Fig 3), and treatment with ethosuximide was started. Both twins were afebrile at the time of the seizures.

Magnetic resonance imaging studies of twin A showed prominent perivascular spaces in deep and subcortical white matter. Images of twin B showed discrete echodense signals in periventricular white matter. The relationship of these nonspecific abnormalities to the twins' generalized seizure disorder is not clear. Both twins had further atypical absence and tonic-clonic seizures. Therefore, treatment with valproate was begun, with subsequent resolution of clinical seizures. The third, dizygotic triplet never had any clinical seizures; an EEG was within normal limits.

COMMENT

The importance of genetic factors in the cause of idiopathic seizures has been recognized as long as convulsions have been viewed as a medical illness.[7] The precise abnormalities that result in genetic seizure disorders are only defined in a very small percentage of cases. One approach to understanding the genetic causes of diverse seizure types is to define the aspects of a seizure disorder that are shared by monozygotic twins with epilepsy. While this does not define precise molecular defects that result in epilepsy, it provides clues as to the aberrant processes that can contribute to this disorder.

The series of monozygotic twins presented here adds to previous surveys of twins with seizures. In this article, 11 sets of monozygotic twins in which one or both twins had nonfebrile, idiopathic seizure(s) were surveyed. In the case of nine sets of twins, both patients had at least one seizure. This very high concordance rate of 82% is similar to previous studies. Furthermore, in pair 7, one of the two instances where one twin has had a seizure and the other has not, the asymptomatic twin had an abnormal EEG, with bursts of generalized spike and wave activity, while the symptomatic twin had a normal EEG. This finding suggests that the "non-epileptic" child shares his twin's propensity for seizures, and that the actual concordance rate is probably greater than 82%.

Studies of monozygotic twins carried out over the last 50 years have shown that 60% to 94% of twins share the propensity for seizures[1-4]; we report a rate of 82%. Since the retrospective study presented here depends on clinicians' memories of twins they have treated, the pairs presented could be biased in favor of twins concordant for seizures. However, the concordance rate found in this study agrees with previous studies that do not suffer from this potential bias.[1-4] This implies that this bias is unlikely to be of major significance. The concordance rate in dizygotic twins was not investigated here, but has been previously shown to be considerably lower, at 23.8% in one study.[3] Set 4, with monozygotic girls, both with seizures, and a dizygotic boy without a seizure disorder demonstrates well the higher concordance in monozygotic twins. The fact that there is such a high rate of concordance in monozygotic twins emphasizes the major role of genetics in idiopathic epilepsy.

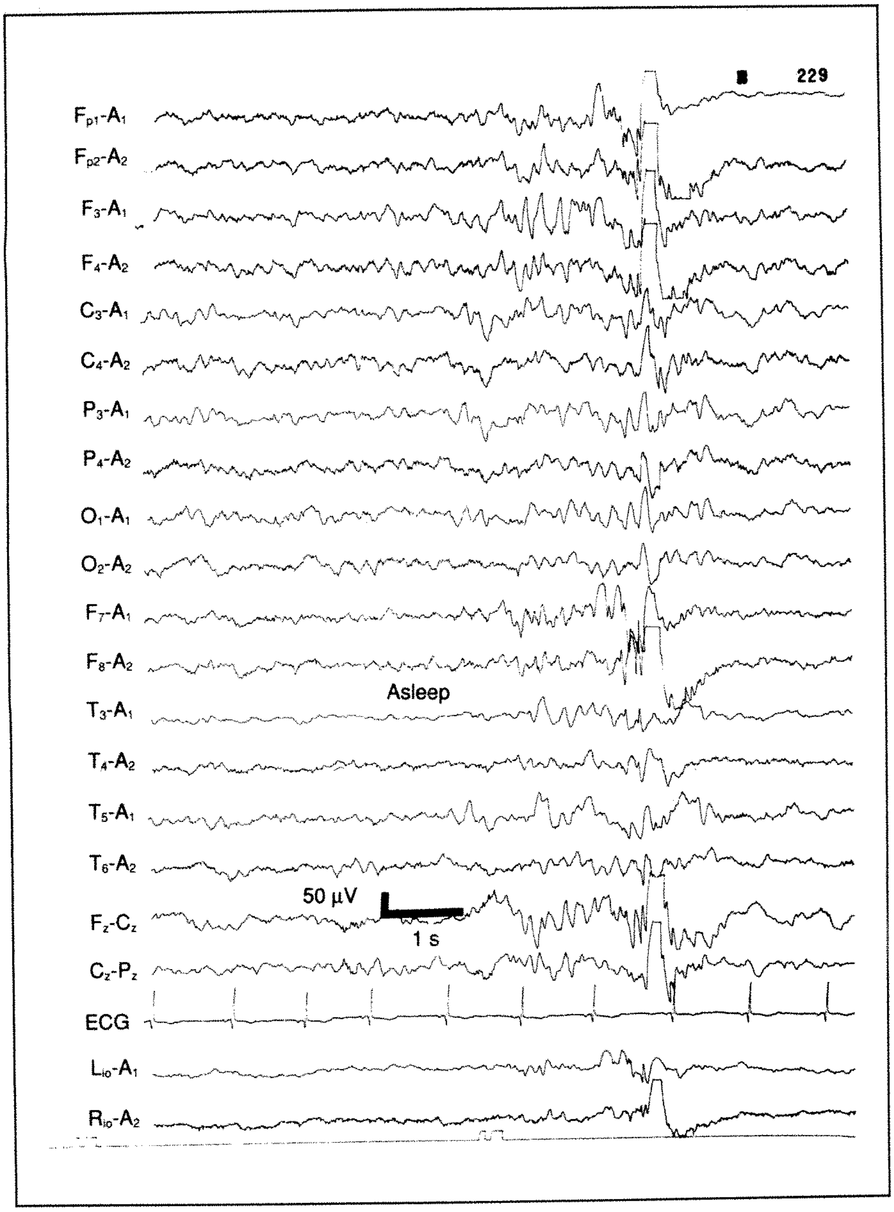


Fig 2.—Portion of electroencephalogram from set 4, twin A, at 5 years of age. Note generalized spike and wave activity. ECG indicates electrocardiogram.

While documenting the high concordance for seizures in monozygotic twins is important for underlining the major role of genetics in idiopathic seizures, an assessment of other features of the twins' seizures may help identify abnormalities that can result in seizures. In our series, the monozygotic twins share not only the propensity for seizures, they also display similar seizure types, and have similar EEGs. In all sets, whether the seizures were focal (ie, pairs 1 and 2) or generalized, the clinical presentations were similar in each set of twins. The EEG patterns, whether generalized or focal, were also strikingly similar. In both of the pairs where there was a focal area of discharge, the location of the focal abnormality was the same (Fig 1).

Previous authors have investigated the similarity between the seizure types and the EEG patterns in epileptic twins. Seizure manifestations are similar in 70% to 100% of twins with primary generalized seizures—whether tonic-clonic, absence, or myoclonic.[1,8] One of the pairs presented here (pair 1) also demonstrates the concordance of seizure type in twins with infantile spasms and West syndrome. There is one previously documented pair of identical twins, both of whom had infantile spasms.[9] Our series of twins further demonstrates that the clinical type of generalized seizure is subject to genetic control.

While genetic factors have been known to be of importance in generalized seizures for some time, the importance of heredity in partial seizures has only been recognized more recently, with evidence of familial clustering of EEG centrotemporal discharges and of Rolandic seizures.[10,11] One study of a single pair of monozygotic twins with partial complex seizures found that the twins shared the seizure manifestations as well as the focal discharges on EEG.[12] Our series provides another case of partial complex seizures in monozygotic twins where the clinical and the electrical abnormalities are strikingly similar (pair 2). An additional pair (pair 1) involves twins with both generalized and partial seizures. In these sets, the clinical manifestations of the partial seizures were similar, and the location of focal discharges on EEGs were the same (Fig 1). This series of twins adds to the growing recognition of the importance of heredity in partial as well as generalized seizures. The fact that the location of abnormal electrical discharges is shared in twins prompts attention to the role of genetics in focal maldevelopment.

Prior studies of twins with seizures have not focused on the response to medications or on the degree of control achieved. In seven cases in this series, seizures were controlled in both twins by the same medication regimen. In the two pairs with myoclonic seizures, pairs 3 and 4, clonazepam was initially used for therapy. In each family, only one twin continued to have seizures, and a second medication was added or substituted for that twin, with subsequent improved control.

The most striking feature in this series of epileptic twins is the frequency with which the time of onset was shared by the twins. In three pairs (1, 2, and 3), the first seizures of the twins were synchronous, occurring within 24 hours of each other. The patients were afebrile at the time of their seizures, so a shared infection is unlikely to explain this timing. Furthermore, for all of the twins, both of whom had seizures, the onset of seizures was within 1 year of each other. The mean time between onset of one and the other twins' seizures was 2.3 months in the eight cases that can be analyzed.

Prior studies of twins with seizures have, in general, not compared the age of onset in twins. Lennox[1] and Vercelletto and Courjon[4] each made note of a case in which twins had onset of seizures within 24 hours of each other. They did not, however, discuss the generality of this synchrony or its significance. In one prior series of 19 monozygotic twins, 11 sets had their first seizures within 1 month of each other.[2] In only one pair

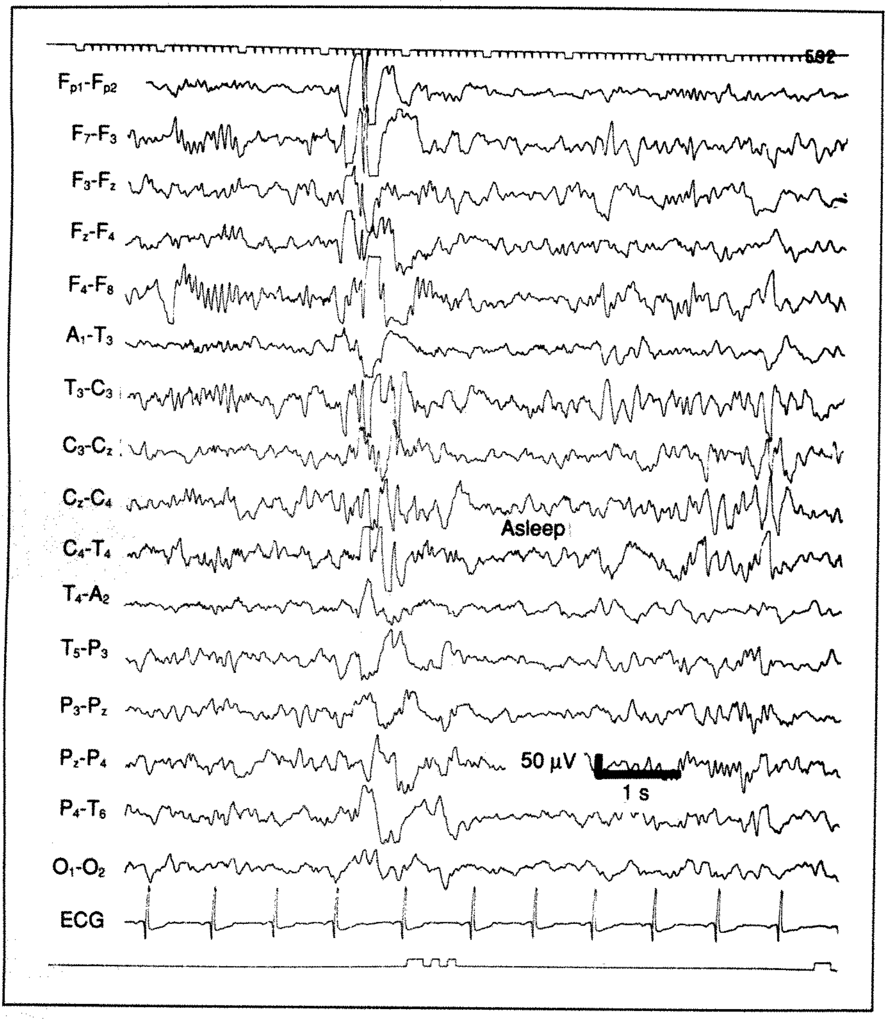


Fig 3.—Portion of electroencephalogram from set 4, twin B, at 5 years of age. Note the generalized spike and wave activity, as in Fig 2. ECG indicates electrocardiogram.

was the first seizure more than 1 year apart; and the mean interval in onset of the cotwins seizures was 6.5 months in the 18 cases of their series that can be analyzed.[2]

The marked synchrony of onset of seizures in monozygous twins suggests that the cause of epilepsy, at least in many cases, is likely to be due to a process that continues in a regulated fashion through postnatal life. Possibilities include myelination, cell death, and synaptic rearrangements. Myelination continues approximately through age 30 years,[13] with myelination of the cortical-connecting fibers a relatively late event. Abnormal myelination could explain either focal or generalized seizures. In pair 1, the abnormal gray-white differentiation seen in imaging studies would be consistent with such an abnormality. Postnatal connections can change through selective neuronal cell death, or through changes in neuronal synapses. Abnormal genetic regulation of either of these two processes could result in the onset of epilepsy at a specific age. Further investigation into genetic control of myelination, cell death, and synaptic reorganization is needed to determine more of the specific abnormalities that can cause epilepsy.

We thank Jane Achenbach-Ng, MD, Charles Barlow, MD, Nancy Canter-Weiner, MD, Gregory Holmes, MD, Jeffrey Macklis, MD, Jeffrey Saver, MD, David Urion, MD, and Lisa Yessayan, MD, for providing us with cases. We thank Gregory Holmes, MD, for providing electroencephalograms of asymptomatic twins. We thank Gregory Holmes, MD, and Joseph Volpe, MD, for their support and their helpful comments on the manuscript.

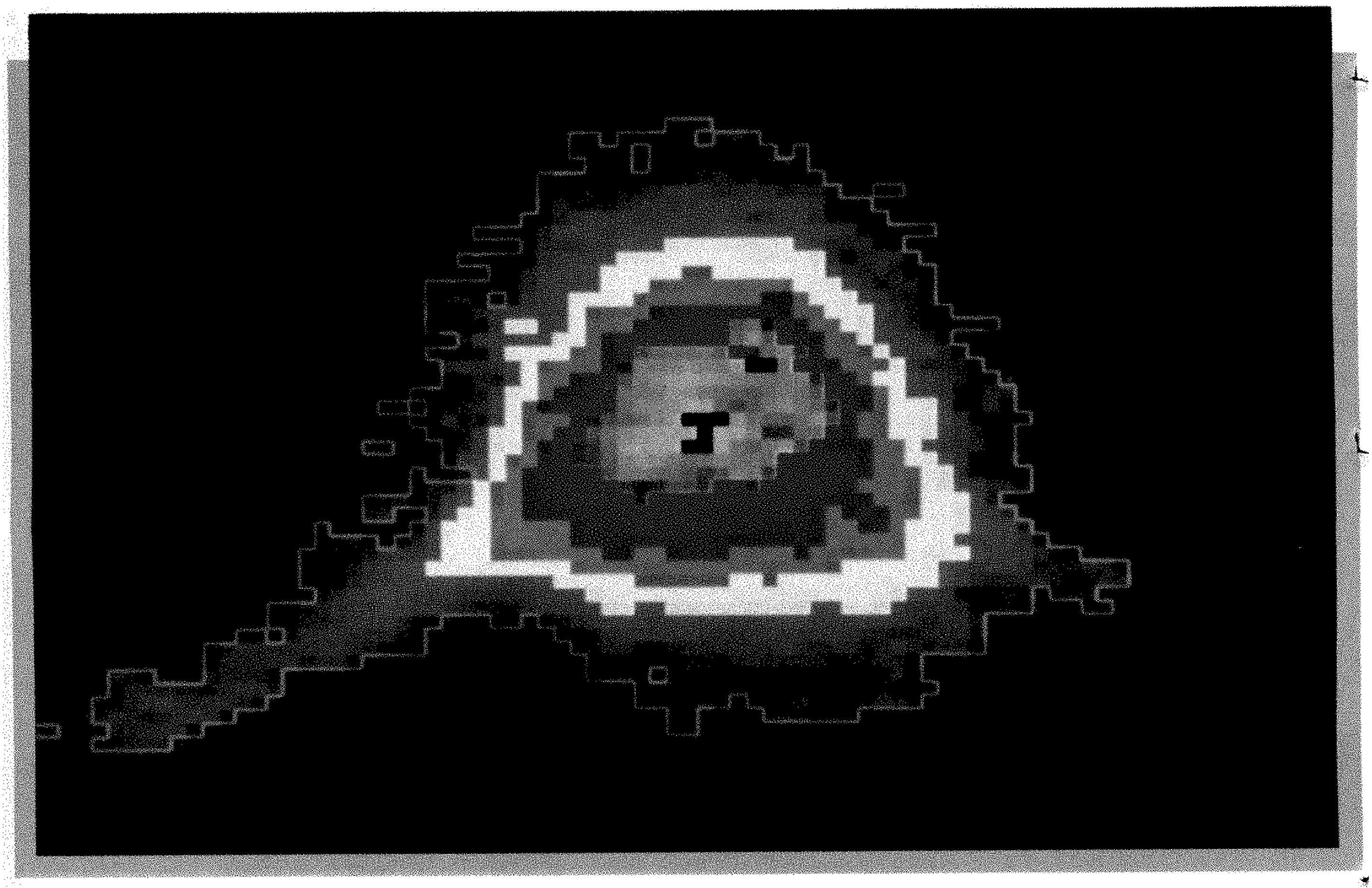
This article is dedicated to the memory of John Barlow.

References

1. Lennox WG. The heredity of epilepsy as told by relatives and twins. *JAMA*. 1951;146:529-536.
2. Gedda L, Tatarelli R. Essential isochronic epilepsy in monozygotic twin pairs. *Acta Genet Med Gemmelol*. 1971;20:380-383.
3. Rosanoff AJ, Handy LM, Rosanoff IA. Etiology of epilepsy. *Arch Neurol Psychiatry*. 1931;31:1165-1193.
4. Vercelletto P, Courjon J. Heredity and generalized epilepsy. *Epilepsia*. 1969;10:7-21.
5. West WJ. On a peculiar form of infantile convulsions. *Lancet*. 1841;1:724-725.
6. Mabry CC, Bautista A, Kirk RFH, Dubilier LD, Braunstein Koepke JA. Familial hyperphosphatasia with mental retardation, seizures, and neurologic deficits. *J Pediatr*. 1970;77:74-85.
7. Doose H, Baier WK. Genetic aspects of childhood epilepsy. *Cleve Clin J Med*. 1983;56:S105-109.
8. Doose H, Baier WK. Epilepsy with primarily generalized myoclonic-astatic seizures: a genetically determined disease. *Eur J Pediatr*. 1987;146:550-554.
9. Pavone L, Mollica F, Incorpora G, Pampiglione G. Infantile spasms syndrome in monozygotic twins: a 7-year follow-up. *Ital J Neurol Sci*. 1985;6:503-506.
10. Bray PF, Wiser WC. Evidence for a genetic etiology of temporal-central abnormalities in focal epilepsy. *N Engl J Med*. 1964;271:926-933.
11. Heijbel J, Blom S, Rasmuson M. Benign epilepsy of childhood with centrotemporal EEG foci: a genetic study. *Epilepsia*. 1975;16:285-293.
12. Hurst R, Lenn NJ. Partial seizures in monozygous twins. *Epilepsia*. 1986;27:121-123.
13. Yakovlev PL, Lecours AR. The myelogenetic cycles of regional maturation of the brain. In: Minkowski A, ed. *Regional Development of the Brain in Early Life*. Boston, Mass: Blackwell Scientific Publications Inc; 1967:3-70.

Current hypotheses suggest

Calcium influx is a key component of ischemic injury[1-4]

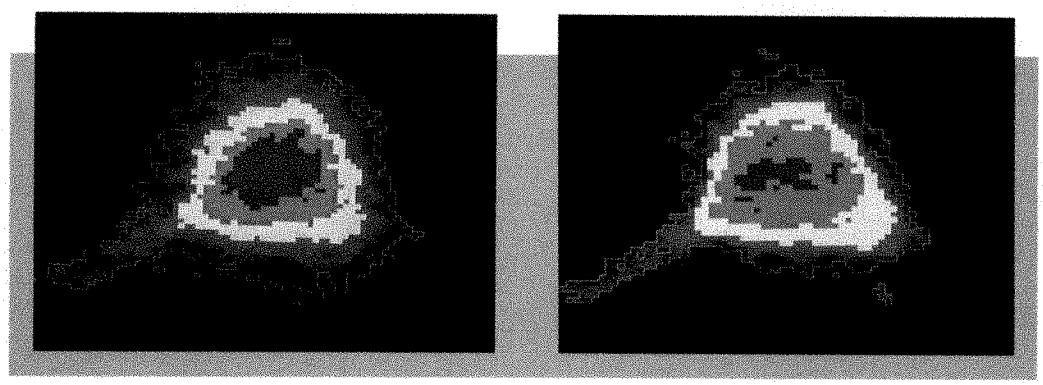


Photomicrograph of depolarized cultured rat hippocampal neuron, showing elevated intracellular calcium. Blue represents lowest and gray represents highest concentration of metabolically active ionized calcium.

Ischemia is associated with calcium influx which activates phospholipases and degrades neuronal cell membranes[2-4]

Cerebroselective calcium channel blockade may protect against ischemic injury

NIMOTOP modulates calcium influx to promote cerebral perfusion and may directly protect neurons[5-7]



Nimodipine-treated cultured rat hippocampal neuron under depolarizing conditions, showing decreased intracellular calcium.

Cultured rat hippocampal neuron showing normal intracellular calcium.[8]

In aneurysmal subarachnoid hemorrhage

CEREBROSELECTIVE

NIMOTOP®

nimodipine/Miles

CAPSULES 30 mg

Reduces the consequences of cerebral ischemia

In aneurysmal subarachnoid hemorrhage

CEREBROSELECTIVE

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Reduces the consequences of cerebral ischemia

BRIEF SUMMARY
NIMOTOP® (nimodipine/Miles) CAPSULES
For Oral Use

INDICATIONS AND USAGE

Nimotop® (nimodipine) is indicated for the improvement of neurological deficits due to spasm following subarachnoid hemorrhage from ruptured congenital intracranial aneurysms in patients who are in good neurological condition post-ictus (e.g. Hunt and Hess Grades I-III). Oral Nimotop® therapy should begin within 96 hours of the subarachnoid hemorrhage and continue for 21 days.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General: Blood Pressure: Nimodipine has the hemodynamic effects expected of a calcium channel blocker, although they are generally not marked. In patients with subarachnoid hemorrhage given Nimotop® in clinical studies, about 5% were reported to have had lowering of the blood pressure and about 1% left the study because of this (not all could be attributed to nimodipine). Nevertheless, blood pressure should be carefully monitored during treatment with Nimotop® based on its known pharmacology and the known effects of calcium channel blockers.

Hepatic Disease: The metabolism of Nimotop® is decreased in patients with impaired hepatic function. Such patients should have their blood pressure and pulse rate monitored closely and should be given a lower dose (see Dosage and Administration).

Laboratory Test Interactions: None known.

Drug Interaction: It is possible that the cardiovascular action of other calcium channel blockers could be enhanced by the addition of Nimotop®.

In Europe, Nimotop® was observed to occasionally intensify the effect of antihypertensive compounds taken concomitantly by patients suffering from hypertension: this phenomenon was not observed in North American clinical trials.

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study, higher incidences of adenocarcinoma of the uterus and Leydig-cell adenoma of the testes were observed in rats given a diet containing 1800 ppm nimodipine (equivalent to 91 to 121 mg/kg/day nimodipine) than in placebo controls. The differences were not statistically significant; however, the higher rates were well within historical control range for these tumors in the Wistar strain. Nimodipine was found not to be carcinogenic in a 91-week mouse study but the high dose of 1800 ppm nimodipine-in-feed (546 to 774 mg/kg/day) shortened the life expectancy of the animals. Mutagenic studies, including the Ames, micronucleus and dominant lethal tests were negative.

Nimodipine did not impair the fertility and general reproductive performance of male and female Wistar rats following oral doses of up to 30 mg/kg/day when administered daily for more than 10 weeks in the males and 3 weeks in the females prior to mating and continued to day 7 of pregnancy. This dose in a rat is about 4 times the equivalent clinical dose of 60 mg q4h in a 50 kg patient.

Pregnancy: Pregnancy Category C. Nimodipine has been shown to have a teratogenic effect in Himalayan rabbits. Incidences of malformations and stunted fetuses were increased at oral (by gavage) doses of 1 and 10 mg/kg/day administered from day 6 through day 18 of pregnancy but not at 3.0 mg/kg/day in one of two identical rabbit studies. In the second study an increased incidence of stunted fetuses was seen at 1.0 mg/kg/day but not at higher doses. Nimodipine was embryotoxic, causing resorption and stunted growth of fetuses, in Long Evans rats at 100 mg/kg/day administered by gavage from day 6 through day 15 of pregnancy. In two other rat studies, doses of 30 mg/kg/day nimodipine administered by gavage from day 16 of gestation and continued until sacrifice (day 20 of pregnancy or day 21 post partum) were associated with higher incidences of skeletal variation, stunted fetuses and stillbirths but no malformations. There are no adequate and well controlled studies in pregnant women to directly assess the effect on human fetuses. Nimodipine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus,

Nursing Mothers: Nimodipine and/or its metabolites have been shown to appear in rat milk at concentrations much higher than in maternal plasma. It is not known whether the drug is excreted in human milk. Because many drugs are excreted in human milk, nursing mothers are advised not to breast feed their babies when taking the drug.

Pediatric Use: Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Adverse experiences were reported by 92 of 823 patients with subarachnoid hemorrhage (11.2%) who were given nimodipine. The most frequently reported adverse experience was decreased blood pressure in 4.4% of these patients. Twenty-nine of 479 (6.1%) placebo treated patients also reported adverse experiences. The events reported with a frequency greater than 1% are displayed below by dose.

DOSE q4h
Number of Patients (%)

	Nimodipine					Placebo
Sign/Symptom	**0.35 mg/kg (n = 82)**	**30 mg (n = 71)**	**60 mg (n = 494)**	**90 mg (n = 172)**	**120 mg (n = 4)**	**(n = 479)**
Decreased Blood Pressure	1 (1.2)	0	19 (3.8)	14 (8.1)	2 (50.0)	6 (1.2)
Abnormal Liver Function Test	1 (1.2)	0	2 (0.4)	1 (0.6)	0	7 (1.5)
Edema	0	0	2 (0.4)	2 (1.2)	0	3 (0.6)
Diarrhea	0	3 (4.2)	0	3 (1.7)	0	3 (0.6)
Rash	2 (2.4)	0	3 (0.6)	2 (1.2)	0	3 (0.6)
Headache	0	1 (1.4)	6 (1.2)	0	0	1 (0.2)
Gastrointestinal Symptoms	2 (2.4)	0	0	2 (1.2)	0	0
Nausea	1 (1.2)	1 (1.4)	6 (1.2)	1 (0.6)	0	0
Dyspnea	1 (1.2)	0	0	0	0	0
EKG Abnormalities	0	1 (1.4)	0	1 (0.6)	0	0
Tachycardia	0	1 (1.4)	0	0	0	0
Bradycardia	0	0	5 (1.0)	1 (0.6)	0	0
Muscle Pain/Cramp	0	1 (1.4)	1 (0.2)	1 (0.6)	0	0
Acne	0	1 (1.4)	0	0	0	0
Depression	0	1 (1.4)	0	0	0	0

There were no other adverse experiences reported by the patients who were given 0.35 mg/kg q4h, 30 mg q4h or 120 mg q4h. Adverse experiences with an incidence rate of less than 1% in the 60 mg q4h dose group were: hepatitis; itching; gastrointestinal hemorrhage; thrombocytopenia; anemia; palpitations; vomiting; flushing; diaphoresis; wheezing; phenytoin toxicity; lightheadedness; dizziness; rebound vasospasm; jaundice; hypertension; hematoma.

Adverse experiences with an incidence rate less than 1% in the 90 mg q4h dose group were: itching; gastrointestinal hemorrhage; thrombocytopenia; neurological deterioration; vomiting; diaphoresis; congestive heart failure; hyponatremia; decreasing platelet count; disseminated intravascular coagulation; deep vein thrombosis.

As can be seen from the table, side effects that appear related to nimodipine use based on increased incidence with higher dose or a higher rate compared to placebo control, included decreased blood pressure, edema and headaches which are known pharmacologic actions of calcium channel blockers. It must be noted, however, that SAH is frequently accompanied by alterations in consciousness which lead to an under reporting of adverse experiences. Patients who received nimodipine in clinical trials for other indications reported flushing (2.1%), headache (4.1%) and fluid retention (0.3%), typical responses to calcium channel blockers. As a calcium channel blocker, nimodipine may have the potential to exacerbate heart failure in susceptible patients or to interfere with A-V conduction, but these events were not observed.

No clinically significant effects on hematologic factors, renal or hepatic function or carbohydrate metabolism have been causally associated with oral nimodipine. Isolated cases of non-fasting elevated serum glucose levels (0.8%), elevated LDH levels (0.4%), decreased platelet counts (0.3%), elevated alkaline phosphatase levels (0.2%) and elevated SGPT levels (0.2%) have been reported rarely.

OVERDOSAGE

There have been no reports of overdosage from the oral administration of Nimotop®. Symptoms of overdosage would be expected to be related to cardiovascular effects such as excessive peripheral vasodilation with marked systemic hypotension. Clinically significant hypotension due to Nimotop® overdosage may require active cardiovascular support. Norepinephrine or dopamine may be helpful in restoring blood pressure. Since Nimotop® is highly protein-bound, dialysis is not likely to be of benefit.

DOSAGE AND ADMINISTRATION

Nimotop® is given orally in the form of ivory colored, soft gelatin 30 mg capsules for subarachnoid hemorrhage.

The oral dose is 60 mg (two 30 mg capsules) every 4 hours for 21 consecutive days. Oral Nimotop® therapy should commence within 96 hours of the subarachnoid hemorrhage.

If the capsule cannot be swallowed, e.g., at the time of surgery, or if the patient is unconscious, a hole should be made in both ends of the capsule with an 18 gauge needle, and the contents of the capsule extracted into a syringe. The contents should then be emptied into the patient's *in situ* naso-gastric tube and washed down the tube with 30 mL of normal saline (0.9%).

Patients with hepatic failure have substantially reduced clearance and approximately doubled C_{max}. Dosage should be reduced to 30 mg every 4 hours, with close monitoring of blood pressure and heart rate.

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REFERENCES: **1.** Gelmers HJ. The role of calcium and the significance of calcium antagonists in some neurological and neurosurgical diseases. *Clin Neurol Neurosurg.* 1983;85:213-224. **2.** Siesjö BK. Calcium, ischemia, and death of brain cells. *Ann NY Acad Sci.* 1988;522:638-661. **3.** Hoff JT. Cerebral protection. *J Neurosurg.* 1986;65:579-591. **4.** Hubschmann OR. The role of calcium in parenchymal cell injury in subarachnoid haemorrhage. *Neurolog Res.* 1987;9:265-269. **5.** Scriabine A, van den Kerckhoff W. Pharmacology of nimodipine. A review. *Ann NY Acad Sci.* 1988;522:698-706. **6.** Petruk KC, West M, Mohr G. Nimodipine treatment in poor-grade aneurysm patients. Results of a multicenter double-blind placebo-controlled trial. *J Neurosurg.* 1988;68:505-517. **7.** Uematsu D, Greenberg JH, Hickey WF, Reivich M. Nimodipine attenuates both increase in cytosolic free calcium and histologic damage following focal cerebral ischemia and reperfusion in cats. *Stroke.* 1989;20:1531-1537. **8.** Data on file, Miles Inc.

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Tremor at Onset

Predictor of Cognitive and Motor Outcome in Parkinson's Disease?

Linda A. Hershey, MD, PhD; Brian J. Feldman, MD; Kye Y. Kim, MD; Chris Commichau; David G. Lichter, MD

• We examined 46 male patients with idiopathic Parkinson's disease to see whether tremor at onset was as useful a predictor of benign clinical outcome as tremor predominance after several years. When we compared patients with tremor at onset (n = 27) with those whose disease began with bradykinesia/rigidity (n = 9), or gait disorder (n = 10), we found no significant differences after a mean of 7 years in motor, cognitive, or affective status. Sixteen of the tremor-onset patients continued to have tremor predominance with minimal gait disorder after about 7 years. These tremor-predominant patients had significantly better motor outcome and somewhat better cognitive outcome than either tremor-onset patients who subsequently developed gait disorder (n = 11) or patients without tremor at onset (n = 19). Tremor predominance after several years appears to be a better predictor of a benign clinical course of Parkinson's disease than tremor at onset.

(*Arch Neurol.* 1991;48:1049-1051)

Patients with Parkinson's disease (PD) who continue to have tremor predominance after 2 to 7 years have been found to develop less motor and functional impairment than those with predominance of rigidity, bradykinesia, or gait disorder.[1-5] This finding has been used to argue the possibility of two subtypes of PD, with differences in underlying pathophysiologic features. Huber and others[4] suggested that patients with tremor at onset be compared longitudinally with those whose onset was characterized by rigidity, bradykinesia, or gait disorder.

Several studies[3,4,6,7] have shown that cognitive impairment varies inversely with tremor severity in PD, while others[8,9] have found a positive correlation. In one large cohort of patients with early PD, no significant difference was found when cognitive performance of the tremor-predominant group was compared with that of the group with postural instability and gait disorder.[5]

Depression is seen in 10% to 70% of PD patients,[10] and it is positively correlated with motor dysfunction, according to some.[11-14] Others,[4,15-19] however, report the lack of correlation between motor and affective dysfunction in PD.

We examined a broad spectrum of PD patients to see whether tremor at onset was as accurate a predictor of good motor outcome as was tremor predominance after several years. We also assessed the cognitive and affective status of these patients, looking for correlations with tremor predominance.

PATIENTS AND METHODS

Patients

Forty-six men over the age of 40 years with idiopathic PD gave written informed consent to participate in this study soon after they were enrolled in a newly established Movement Disorders Clinic at the Buffalo (NY) Department of Veterans Affairs Medical Center. The diagnosis of PD was based on the presence of at least two cardinal signs, according to the criteria of Hoehn and Yahr.[2] At the time of enrollment, we inquired about the age and primary symptom at onset of PD (tremor, rigidity, bradykinesia, or gait disorder). Excluded were patients with (1) exposure to neuroleptics, reserpine, or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP); (2) a history of encephalitis; (3) signs of progressive supranuclear palsy, Shy-Drager syndrome, olivopontocerebellar atrophy, or stroke; (4) psychosis or dementia prior to onset of PD; or (5) alcohol/drug abuse within the last 5 years.

Treatment

Thirty-seven of the 46 patients were being treated with carbidopa/levodopa, with or without adjunctive therapies such as bromocriptine (n = 21), amantadine hydrochloride (n = 19), trihexyphenidyl hydrochloride (n = 3), or diphenhydramine hydrochloride (n = 2). Six patients received amantadine without levodopa; one had diphenhydramine alone and two did not yet need pharmacotherapy. Two patients had had essential tremor for several years prior to the onset of PD and were receiving primidone in addition to carbidopa/levodopa and bromocriptine or amantadine. One patient was treated with a standard therapeutic dose of amitriptyline for his depression (150 mg/d), while three others received lower doses (50 mg/d). Patients were stabilized using doses of antiparkinsonian therapy that seemed optimal for them for at least 1 month prior to enrollment into this study.

Clinical Assessment

Severity of parkinsonism was graded by the 0 through 5 functional staging system of Hoehn and Yahr[2] and a modified Columbia scale,[20] where each of 12 parkinsonian signs (dysarthria, facial masking, rest tremor, postural tremor, rigidity, bradykinesia, finger-tap frequency, foot-tap frequency, rising from a chair, posture, postural instability, and gait disorder) was rated on a 0-through-4-point scale. Ability to perform activities of daily living was assessed by asking the patient's spouse or next of kin the 10 questions of the Barthel Index.[21] Total scores on this measure varied from 0 (totally dependent) to 100 (totally independent).

Cognitive Assessment

The presence of dementia was determined using the *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised* (*DSM-III-R*) criteria.[22] Severity of cognitive dysfunction was estimated using the 30-question Cognitive Capacity Screening Examination of Jacobs and others,[23] on which the potential range of scores was 0 (no correct answers) to 30 (perfect score). A Cognitive Capacity Screening Examination score of 20 or less has been correlated with the presence of dementia by *DSM-III* criteria in PD patients as well as in those with other neurodegenerative disorders.[24] Severity of cognitive impairment was also assessed by interviewing the patients' surrogate with the 10-question Functional Activities Questionnaire of Pfeffer and others,[25] on which the potential range of scores was 0 (no functional impairment) to 30 (total dependence on others). On this scale, the cut-off score for Parkinson's dementia according to *DSM-III* criteria is 12 or more.[26]

Affective Assessment

The presence of major depression or dysthymia was determined using *DSM-III-R* criteria.[22] Severity of depression was graded on a scale of 0 (no affective symptoms) to 62 (most severe symptoms), using the 21-item Hamilton Rating Scale for Depression.[27] Patients rated the severity of their own affective symptoms on the 20-question Zung Self-Rating Scale,[28] on which raw scores ranged from 20 (no affective symptoms) to 80 (most severe symptoms).

Accepted for publication April 4, 1991.

From the Departments of Neurology (Drs Hershey and Lichter) and Psychiatry (Dr Kim), Department of Veterans Affairs Medical Center and State University of New York at Buffalo. Dr Feldman and Mr Commichau were students working in the Neurology Department at the time of this study.

Presented, in part, at the First International Congress of Movement Disorders, Washington, DC, April 25, 1990.

Reprint requests to Department of Neurology, 3495 Bailey Ave, Buffalo, NY 14215 (Dr Hershey).

Statistical Analysis

We used analysis of variance to compare means of continuous variables in the three symptom-onset groups. Comparisons of ordinal data (Hoehn and Yahr stages) from the three groups were performed with the Kruskal-Wallis test. Results in Tables 1 through 4 were expressed as the mean ± 1 SD.

RESULTS

Twenty-seven patients experienced tremor as the earliest symptom of their PD; nine noted rigidity or bradykinesia, and 10 complained of gait disorder at onset. Patients ranged in age from 43 to 77 years (mean age, 68.0 years) at the time of examination, while age at onset ranged from 25 to 75 years (mean age, 59.9 years). Neither age at disease onset nor age at examination differed significantly among the three symptom-onset groups (Table 1).

The groups did not differ with respect to total years of education (mean, 11.8 years; range, 5 to 19 years) or duration of parkinsonism (mean, 8.1 years; range, 1 to 35 years). The range of daily doses of levodopa was from 200 to 1500 mg/d (mean dose, 705 mg/d). There was a trend for the mean daily levodopa dose to be lower in the group with tremor at onset, but between-group differences were not statistically significant (Table 1), neither were there significant differences in mean daily doses of bromocriptine or amantadine.

Patients in this study encompassed a broad spectrum of Hoehn and Yahr stages (mean, 3.0; range, 1 to 4). When motor and functional outcome measures were compared among the three symptom-onset groups, no significant differences were found (Table 2). There were also no significant differences in measures of cognitive and affective status (Table 2). Three patients with tremor at onset met *DSM-III-R* criteria for dementia by the time of enrollment. These three had also developed a significant gait disorder. Two patients whose PD had begun with rigidity and two with gait disorder also met the criteria for dementia.

Table 1.—Clinical Features According to Symptom at Onset

Clinical Feature	Symptom at Onset Tremor	Rigidity or Bradykinesia	Gait Disorder
n	27	9	10
Age at examination, y	67.7 ± 7.2	68.8 ± 5.8	68.0 ± 5.2
Age at onset, y	60.5 ± 9.0	57.1 ± 8.6	60.7 ± 4.3
Education, y	11.9 ± 2.8	12.1 ± 3.4	11.0 ± 2.4
Duration of disease, y	7.2 ± 6.2	11.7 ± 9.8	7.3 ± 3.4
Levodopa dose, mg	589 ± 274	881 ± 386	794 ± 396
Bromocriptine dose, mg	9.0 ± 3.2	10.8 ± 6.3	12.0 ± 10.5
Amantadine dose, mg	240 ± 52	250 ± 71	275 ± 50

Table 2.—Outcome Measures According to Symptom at Onset

Outcome Measure*	Symptom at Onset Tremor	Rigidity or Bradykinesia	Gait Disorder
n	27	9	10
Hoehn and Yahr stage (0-5)	2.8 ± 0.7	3.2 ± 0.7	3.2 ± 0.9
Columbia Scale (0-48)	15.9 ± 6.2	17.2 ± 6.7	18.1 ± 5.8
Barthel Index (0-100)	91.1 ± 16.5	84.4 ± 18.4	84.0 ± 16.1
CCSE (0-30)	23.8 ± 4.8	22.8 ± 4.7	23.5 ± 4.5
FAQ (0-30)	3.8 ± 5.8	9.6 ± 8.8	7.2 ± 8.0
HRSD (0-62)	11.8 ± 7.3	14.0 ± 8.3	13.3 ± 5.5
ZSRS (20-80)	45.5 ± 20.7	59.4 ± 30.2	56.1 ± 24.1

*CCSE indicates Cognitive Capacity Screening Examination; FAQ, Functional Activities Questionnaire; HRSD, Hamilton Rating Scale for Depression; and ZSRS, Zung Self-Rating Scale. Numbers in parentheses indicate potential ranges of scores.

Table 3.—Clinical Features According to Tremor Predominance

Clinical Feature	Tremor at Onset With Tremor Predominance	Tremor at Onset With Eventual Gait Disorder	Rigidity, Bradykinesia, Gait at Onset
n	16	11	19
Age at examination, y	66.8 ± 7.7	69.0 ± 6.6	68.4 ± 5.4
Age at onset, y	59.9 ± 10.0	61.4 ± 7.9	59.0 ± 6.8
Education, y	12.5 ± 3.2	11.1 ± 1.9	11.5 ± 2.9
Duration of disease, y	6.9 ± 7.2	7.6 ± 4.5	9.4 ± 7.4
Levodopa dose, mg	635 ± 251	539 ± 304	835 ± 382
Bromocriptine dose, mg	10.5 ± 2.7	7.5 ± 3.1	11.4 ± 8.0
Amantadine dose, mg	250 ± 55	225 ± 50	267 ± 52

Patients were regrouped according to historical information about symptoms at onset and objective findings at the time of enrollment. Those with tremor at onset were divided into two groups. One group of 16 patients with tremor at onset still had tremor predominance at the time of examination (gait scores, 0/4 to 1/4). Another group of 11 patients had had tremor at onset, but their gait scores were 2/4 to 3/4 by the time of enrollment. Data from the 19 patients whose disease had begun with rigidity, bradykinesia, or gait disorder were pooled for this comparison (Table 3). These three subgroups did not differ with respect to age at examination, age at onset, years of education, duration of disease, or mean daily doses of antiparkinsonian drugs.

Tremor-onset patients who continued to have tremor predominance after about 7 years had significantly milder motor function than did the others, according to measures such as the Hoehn and Yahr stage, modified Columbia scale, and Barthel Index (Table 4). While no significant differences were found among the three groups in mean Cognitive Capacity Screening Examination scores, patients with tremor predominance had statistically better cognitive function as reflected by Functional Activities scores (Table 4). None of the seven demented patients in this series belonged to the tremor-predominant group. No significant affec-

Table 4.—Outcome Measures According to Tremor Predominance

Outcome Measure*	Tremor at Onset With Tremor Predominance	Tremor at Onset With Eventual Gait Disorder	Rigidity, Bradykinesia, Gait at Onset
n	16	11	19
Hoehn and Yahr stage (0-5)	2.5 ± 0.6†	3.3 ± 0.5	3.2 ± 0.8
Columbia Scale (0-48)	12.4 ± 3.5‡	20.6 ± 5.8	17.7 ± 6.1
Barthel Index (0-100)	96.6 ± 6.2§	83.2 ± 23.0	84.2 ± 16.8
CCSE (0-30)	25.2 ± 2.9	21.7 ± 6.3	23.2 ± 4.5
FAQ (0-30)	2.1 ± 2.2§	6.3 ± 8.2	8.3 ± 8.2
HRSD (0-62)	12.9 ± 8.7	10.2 ± 4.8	13.6 ± 6.8
ZSRS (20-80)	45.9 ± 22.3	44.8 ± 19.1	57.7 ± 26.4

*CCSE indicates Cognitive Capacity Screening Examination; FAQ, Functional Activities Questionnaire; HRSD, Hamilton Rating Scale for Depression; and ZSRS, Zung Self-Rating Scale. Numbers in parentheses indicate potential ranges of scores.

†$P < .02$ by Kruskal-Wallis one-way analysis of variance.

‡$P < .001$ by analysis of variance.

§$P < .05$ by analysis of variance.

tive differences were found among these subgroups, according to the Hamilton Rating Scale for Depression and the Zung Self-Rating Scale scores (Table 4). Ten of the 46 patients satisfied the *DSM-III-R* criteria for major depression and four met the criteria for dysthymia.

COMMENT

We found that tremor predominance after about 7 years was a statistically significant predictor of good motor outcome in men with PD, while tremor at onset was not. This finding appeared to be independent of important variables such as age at onset and duration of disease. Tremor predominance after 5 to 7 years has already been shown to be associated with a more benign clinical course, but these studies did not examine symptoms at onset.[1-4] In the DATATOP cohort, tremor predominance after about 2 years was a statistically significant predictor of good motor outcome, even though tremor at onset was not.[5]

According to our data, tremor at onset does not necessarily predict good cognitive outcome, even though tremor predominance after 7 years does. None of our 16 tremor-predominant patients had developed dementia by the time of examination, while three of our tremor-onset patients had. Jankovic and others[5] also reported the lack of correlation between cognitive performance and type of symptoms at onset, although their sample was limited to patients with early PD and excluded those with significant cognitive impairment. Our data also agree with those of Huber and others,[4] who showed a significant correlation between tremor predominance after several years and good cognitive outcome.

Neither tremor at onset nor tremor predominance appeared to be a good predictor of affective outcome in men with PD. We also found no significant correlation between individual measures of motor and affective dysfunction. These observations are consistent with the findings of others,[4,15-19] and they support the hypothesis that there is a pathophysiologic distinction between motor and affective dysfunction in PD.

Anatomical and biochemical heterogeneity in PD has been suggested by various autopsy-based studies.[29,30] Future studies using positron emission tomography may show different patterns of 18-fluorodopa uptake in tremor-onset patients who develop early gait disorder and impairment of cognitive function, compared with those who do not.

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References

1. Schwab RS, Englund AC, Peterson E. Akinesia in Parkinson's disease. *Neurology.* 1959;9:65-72.
2. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;17:427-442.
3. Zetusky WJ, Jankovic J, Pirozzolo FJ. The heterogeneity of Parkinson's disease: clinical and prognostic implications. *Neurology.* 1985;35:522-526.
4. Huber SJ, Paulson GW, Shuttleworth EC. Relationship of motor symptoms, intellectual impairment, and depression in Parkinson's disease. *J Neurol Neurosurg Psychiatry.* 1988;51:855-858.
5. Jankovic J, McDermott M, Carter J, et al. Variable expression of Parkinson's disease: a baseline analysis of the DATATOP cohort. *Neurology.* 1990;40:1529-1534.
6. Lieberman AN. Parkinson's disease: a clinical review. *Am J Med Sci.* 1974;267:66-80.
7. Mortimer JA, Pirozzolo FJ, Hansch EC, Webster DD. Relationship of motor symptoms to intellectual deficits in Parkinson's disease. *Neurology.* 1982;32:133-137.
8. Martilla RJ, Rinne UK. Dementia in Parkinson's disease. *Acta Neurol Scand.* 1976;54:431-441.
9. Reid W, Hely MA, Morris JGL, et al. The evolution of dementia in idiopathic Parkinson's disease: neuropsychological and clinical evidence in support of subtypes. *Mov Disord.* 1990;5 (suppl 1):71.
10. Rondot P, deRecondo J, Coignet A, Ziegler M. Mental disorders in Parkinson's disease after treatment with L-dopa. *Adv Neurol.* 1984;40:259-269.
11. Mindham RHS, Marsden CD, Parkes JD. Psychiatric symptoms during L-dopa therapy for Parkinson's disease and their relationship to physical disability. *Psychol Med.* 1976;6:23-33.
12. Mayeux R, Stern Y, Rosen J, Leventhal J. Depression, intellectual impairment, and Parkinson's disease. *Neurology.* 1981;31:645-650.
13. Gotham AM, Brown RG, Marsden CD. Depression in Parkinson's disease: a quantitative and qualitative analysis. *J Neurol Neurosurg Psychiatry.* 1986;49:381-389.
14. Starkenstein SR, Preziosi TJ, Bolduc PL, Robinson RG. Depression in Parkinson's disease. *J Nerv Ment Dis.* 1990;178:27-31.
15. Horn S. Some psychological factors in parkinsonism. *J Neurol Neurosurg Psychiatry.* 1974;37:27-31.
16. Celesia GG, Wanamaker WM. Psychiatric disturbances in Parkinson's disease. *Dis Nerv Sys.* 1972;33:577-583.
17. Robbins AH. Depression in patients with parkinsonism. Br J Psychiatry 1976;128:141-145.
18. Santamaria J, Tolosa E, Valles A. Parkinson's disease with depression: a possible subgroup of idiopathic parkinsonism. *Neurology.* 1986; 36:1130-1133.
19. Lichter DG, Corbett AJ, Fitzgibbon GM, et al. Cognitive and motor dysfunction in Parkinson's disease: clinical, performance, and computed tomographic correlations. *Arch Neurol.* 1988;45:854-860.
20. Lesser RP, Fahn S, Snider SR, Cote LJ, Isgreen WP, Barrett RE. Analysis of the clinical problems in parkinsonism and the complications of long-term levodopa therapy. *Neurology.* 1979; 29:1253-1260.
21. Barthel DW, Mahoney FI. Functional evaluation: Barthel index. *Md State Med J.* 1965;14:61-65.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised.* Washington, DC: American Psychiatric Association; 1987.
23. Jacobs JW, Bernhard MR, Delgado A, Strain JJ. Screening for organic mental syndromes in the medically ill. *Ann Intern Med.* 1977;86:40-45.
24. Hershey L, Grossniklaus D, Whicker L. Screening for cognitive impairment. *JAMA.* 1982;248:1975.
25. Pfeffer RI, Kurosaki TT, Harrah CH, et al. Measurement of functional activities in older adults in the community. *J Gerontol.* 1982;37:323-329.
26. Hershey LA, Yang SL, Jaffe DF. Usefulness of the FAQ in quantifying functional impairment in demented patients. *Neurology.* 1985; 35(suppl 1):184.
27. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23:56-62.
28. Zung WWK. A self-rating depression scale. *Arch Gen Psychiatry.* 1965;12:63-70.
29. Rinne JO, Rummukainen J, Paljarvi L, Rinne UK. Dementia in Parkinson's disease is related to neuronal loss in the medial substantia nigra. *Ann Neurol.* 1989;26:47-50.
30. Birnheimer H, Birkmayer W, Hornykiewicz O, Jellinger K, Seitelberger F. Brain dopamine and the syndromes of Parkinson and Huntington. *J Neurol Sci.* 1973;20:415-455.

Tritiated Imipramine Binding

A Peripheral Marker for Serotonin in Parkinson's Disease

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• Tritiated imipramine binding in platelets has been used to evaluate serotonin activity in depression in previous studies. This article examined this marker as a possible measure of central nervous system serotonergic activity for depression in patients with Parkinson's disease (PD). The number of binding sites was significantly lower in depressed patients with PD than in a healthy control group. Patients with PD who were not depressed had lower values than the comparison group, but this difference was not significant. We also found a significant correlation between the receptor site values in platelets and cerebrospinal fluid levels of the serotonin metabolite, 5-hydroxyindoleacetic acid ($r = .59$), but this was independent of a diagnosis of depression. Receptor site values were examined to identify appropriate cutoff scores to predict depression in the group of patients with PD. A maximum sensitivity of 50% was achieved with a specificity of 64%. Our results strongly support a generalized alteration in serotonin metabolism in depressed patients with PD, but tritiated imipramine binding in platelets is not a useful diagnostic tool for depression.

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The "serotonin hypothesis" of depression in Parkinson's disease (PD) is based on the evidence of a generalized deficiency of serotonin in patients with PD and depression.[1-5] The cerebrospinal fluid (CSF) concentration of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), is reduced in patients with PD compared with age-matched controls[1]; levels are even lower in patients with depression.[3] Serotonin also plays a role in depression among individuals who do not have PD, since CSF 5-HIAA levels are lower in depressed patients and in suicide victims.[6,7]

An alternative measure of serotonergic function is tritiated imipramine (^{3}H-imipramine) binding, which measures presynaptic serotonergic receptor sites and has been examined in platelets and brain.[8] Tritiated imipramine binding is lower in the platelets of patients without PD but with depression and is reduced in the brains of depressed patients dying of natural causes or suicide when compared with the brains from those who did not commit suicide.[9] However, others have found no difference in brain or platelet binding between depressed and nondepressed individuals.[10,11]

Correlations between platelet and brain ^{3}H-imipramine binding capacity in animal studies[12] suggest that platelet binding may reflect central nervous system activity. Although Raisman et al[13] found ^{3}H-imipramine binding decreased in the brains of patients with PD (in whom depression was not assessed), earlier reports indicated no difference between individuals with PD and controls.[14] Schneider et al[15] found platelet binding reduced in depressed patients with PD. These conflicting studies used small groups and the diagnostic information concerning depression was not systematically obtained.

This study sought to examine the relationship among depression, CSF 5-HIAA, and ^{3}H-imipramine binding in platelets in patients with PD. Second, it sought to determine whether ^{3}H-imipramine binding in platelets could be a sensitive and specific marker for depression in these patients.

SUBJECTS AND METHODS

Patient Group

Seventy patients with idiopathic PD (mean age, 66.9 ± 9.1 years) participated in this study. The diagnosis of idiopathic PD was defined by the presence of at least two of the following four features: tremor, gait disorder, bradykinesia, and rigidity. Clinical history and other physical symptoms had to be consistent with the idiopathic form of the disease. Patients were excluded if there was evidence implicating another cause for the parkinsonism (eg, phenothiazine exposure or history of encephalitis) and if they had taken any type of antidepressant medication or other psychoactive drug in the last 60 days. However, patients who were taking dopamine agonists or dopamine precursors or anticholinergics for PD were included. The type and dose of medication were recorded.

Control Group

This group consisted of 53 age-matched, healthy elderly individuals (mean age, 66.5 ± 4.7 years) who were accompanying patients to the medical center. This included spouses, companions, and significant others who were not blood relatives of the patient group. These individuals were screened to eliminate central nervous system disease, a history of major depression or other psychiatric illness, or other life-threatening medical illnesses. Individuals were excluded if they had taken antidepressant medication within the past 60 days.

Procedures

After giving informed consent all subjects received the following assessments.

Standardized Medical History.—This included a record of all major medical and neurologic problems, psychiatric treatment history, and current medications. For the patients with PD, a detailed history of the onset of the disease was taken and all treatment regimens were recorded.

PD Severity Ratings.—The Unified Parkinson's Disease Rating Scale[16] was used to assess the presence and severity of motor manifestations. Those items that assess mentation, behavior, and mood (items 1 through 4) were excluded because they were measured with alternate instruments described below. The maximum score possible on the remaining items is 172, with higher scores indicating more severe motor disturbance. The Schwab and England[17] inventory of Activities of Daily Living[17] was used. This inventory rates by percentage the degree of independence in Activities of Daily Living, with 100% referring to total independence and 0% indicating the patient is bedridden with impairment of vegetative functions. The Hoehn and Yahr Scale[18] was also completed. This six-stage index ranges from 0 ("no sign of disease") to 5 ("bedridden or wheelchair bound").

Mental Status.—The modified Mini-Mental State Examination was administered to assess intellectual function. This modifica-

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Table 1.—Comparison of Depressed and Nondepressed Patients With Parkinson's Disease (PD) and Healthy Elderly Volunteers*

Group	n	HDRS	Kd	B_{max}
Patients with PD				
Depressed	14	17.4 ± 4.5†	1.6 ± 1.2	740.9 ± 198‡
Nondepressed	56	4.2 ± 3.4	1.6 ± 1.4	862.0 ± 352
Controls	53	4.0 ± 4.2†	2.1 ± 0.8	950.3 ± 255‡

*HDRS indicates Hamilton Depression Rating Scale score; Kd, affinity constant; and B_{max}, number of receptor sites. The total group (patients with PD) was classified as described: depressed, Hamilton Score 12 or more; nondepressed, Hamilton Score less than 12.

†Groups were significantly different ($P < .01$).

‡Groups were significantly different ($P < .05$).

Table 2.—Comparison of Cerebrospinal Fluid (CSF) Metabolites and Binding Measures in Depressed and Nondepressed Patients With Parkinson's Disease*

	Patients With Parkinson's Disease	
	Depressed (n = 8)	Nondepressed (n = 11)
HDRS	16.1 (7.1)†	5.8 (3.6)†
CSF 5-HIAA	14.2 (6.4)	18.8 (6.8)
CSF HVA	52.7 (34.3)	30.5 (12.1)
Kd	1.2 (0.72)	1.5 (0.72)
B_{max}	826.9 (253)	904.2 (384)

*HDRS indicates Hamilton Depression Rating Scale; 5-HIAA, 5-hydroxyindoleacetic acid; HVA, homovanillic acid; Kd, affinity constant; and B_{max}, number of receptor sites. Numbers in parentheses are SDs.

†Groups are significantly different ($P < .01$).

tion of the procedure described by Folstein et al[19] includes additional items that measure naming, language, and attention and has a maximum score of 57. The mean modified Mini-Mental State score for healthy elderly individuals is 52.5 (±4.3).[20]

Psychiatric Evaluation.—A standardized semistructured interview for the Hamilton Depression Rating Scale (HDRS)[21] was administered. Based on previous findings,[1,2] those patients with HDRS scores greater than 12 were classified as clinically depressed.

^{3}H-Imipramine Binding.—Binding of ^{3}H-imipramine in platelets was determined using the method described by Briley et al[22] and modified by Asarch et al.[23]

CSF Studies.—Nineteen of the 70 patients with PD participated in an extended study of biogenic amine metabolites in CSF. These patients were selected because they had cognitive or affective complaints and were admitted to the General Clinical Research Center to complete all assessments. In addition to the HDRS, psychiatric diagnoses for depression were made according to the criteria of the *Diagnostic and Statistical Manual, Revised Third Edition,*[24] using the Structured Clinical Interview[25] completed by a trained interviewer with the patient (and an informant when available).

Lumbar puncture for CSF studies was performed after 18 hours of bed rest. Twenty milliliters of CSF was obtained for biochemical analysis. High-pressure liquid chromatography with amperometric detection was used to measure 5-HIAA and homovanillic acid by a method previously described.[1]

Data Analysis

For ^{3}H-imipramine–binding studies, Scatchard analysis was used to determine the number of receptor sites (B_{max}) and the affinity constant (Kd)[26] for each subject. Tritiated imipramine–binding results were correlated with demographic and disease severity variables. Group mean comparisons were used to examine differences in binding measures between controls and patients. Pearson correlations were used to examine the association between CSF 5-HIAA measures and platelet binding measures. Nonparametric techniques were used to examine the sensitivity and specificity[27] of platelet binding for assessment of depression in PD.

RESULTS

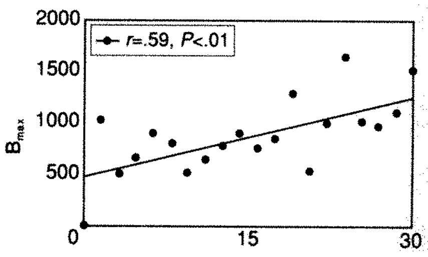
Tritiated imipramine–binding measures for the PD group and the control group were initially compared using a *t* test. This comparison yielded a significant difference between the two groups ($P \leq .05$). Patients with PD were then classified as depressed, using an HDRS score of 12 or greater for depression, or not depressed. The ^{3}H-imipramine–binding measures for the two PD groups and the control group are given in Table 1. An analysis of variance of the B_{max} values yielded a significant F test ($P < .05$) for the comparison of depressed patients with PD, nondepressed patients with PD, and the control group. Post hoc analysis demonstrated significantly lower B_{max} values in the depressed patients with PD than in the controls. The group mean value for the nondepressed patients with PD fell between the other two groups, but was not significantly different from either. Based on effect size reported by Schneider et al,[15] this study had sufficient group size to achieve 65% power for detecting such a difference at the .05 level of significance.

^{3}H-Imipramine–Binding and Disease Severity Measures

The mean duration of illness in the PD group was 8.6 (±2.2) years and the mean Unified Parkinson's Disease Rating Scale score was 41.8 (±26.1). The mean Hoehn and Yahr rating in the PD group was 2.7 (±.79), with 39.1% receiving a score of 1 or 2 (mild disease), 48.4% receiving a score of 3 (moderate severity), and 12.5% receiving a score of 4 or 5 (marked severity). The mean Schwab and England rating was 68.3% (±24.1%) with 23.8% of the patients experiencing serious disability, scoring below 50%. None of these measures were significantly correlated with B_{max} or Kd values.

The mean modified Mini-Mental State score in the PD group was 44.7 (±11.5). This is significantly lower ($P < .05$) than the mean for the control group (52.3 ± 3.4). However, no significant correlation was noted between this measure and B_{max} or Kd values.

Fifty-five (78.6%) patients were taking parkinsonian medication. The correlation between the dose of medication and the B_{max} was not significant ($r = -.2$).



Relationship between the amount of 5-hydroxyindoleacetic acid (5-HIAA) in cerebrospinal fluid (CSF) and the number of tritiated imipramine binding sites in platelets of patients with Parkinson's disease. B_{max} indicates number of receptor sites.

^{3}H-Imipramine–Binding and CSF Measures

Eight (42%) of the 19 patients who had lumbar punctures for the CSF studies were diagnosed as having major depression or dysthymia. They had a mean HDRS score of 16.1 ± 7.1, which represents depression of mild to moderate severity, compared with a mean HDRS score of 5.8 ± 3.6 in the nondepressed patients ($P < .05$). The CSF 5-HIAA and the ^{3}H-imipramine binding values for these patients are given in Table 2. A significant correlation was noted between B_{max} values and CSF 5-HIAA ($r = .59$; $P < .01$) (Figure) but not CSF homovanillic acid ($r = .39$; $P > .1$). The Kd values did not correlate with either CSF metabolite measure.

The mean CSF 5-HIAA level in the depressed group was lower than in the nondepressed group (14.2 ± 6.4 vs 18.8 ± 6.8 ng/mL). This difference was not statistically significant, perhaps due to our small sample size. Based on our previous work,[1] it was estimated that this study yielded low power for this comparison (0.25).

Sensitivity and Specificity of ^{3}H-Imipramine Binding for Depression in PD

The sensitivity and specificity of ^{3}H-imipramine binding to detect depression in PD was examined. A B_{max} cutoff value of 800 correctly classified the maximum number of patients; 37 (53%) of the 70 patients with PD were correctly identified as depressed or not depressed. This value yielded a specificity of 64% and a sensitivity of 50% for depression among the PD group.

COMMENT

This study further supports an alteration in serotonin in PD. First, ^{3}H-imipramine binding in platelets is reduced in patients with PD. A closer examination of these patients demonstrates that patients with depression and PD have significantly fewer binding sites than controls. Patients with PD who were not depressed had BB_{max} values that fell between the controls and the depressed group, although they were not significantly different. Second, platelet binding values significantly correlate with CSF 5-HIAA levels, suggesting that this peripheral measure may reflect central serotonergic activity. Together, these results provide additional evidence for a generalized serotonergic abnormality that may be associated with depression in PD.

The binding values in this study were similar to those reported by Suranyi-Cadotte et al,[14] who found no difference between patients with PD and a comparison group. However, the sample size was much smaller in their study. Schneider and coworkers[15] found a 22% decrease in ^{3}H-imipramine platelet binding in subjects with PD compared with controls. Four of the nine patients with PD had either major depression or dysthymic disorder that may have contributed to the reported difference, although this was not systematically examined. This study demonstrated a 10.9% difference in B_{max} values with a large group size.

This work represents the first report of a correlation between CSF and platelet measures of serotonergic activity. It is usually assumed that CSF markers reflect only nonspecific changes in brain chemistry, but in suicide victims there is a correlation between CSF 5-HIAA and ^{3}H-imipramine–binding sites in the frontal cortex.[28] In depressed patients with PD, Mayberg et al[29] found lowered metabolism in the caudate and in the inferior orbital-frontal cortex, where a serotonergic mechanism for this frontal hypometabolism has been postulated previously.[30] Significant loss of large neurons in the ascending serotonergic pathway of the dorsal raphe nucleus and decreased serotonin concentrations in the projection areas in the frontal cortex have also been reported in patients with PD.[31]

Although pervasive, the serotonergic deficit may not parallel deterioration of the dopamine system. Our previous work indicates no correlation between CSF 5-HIAA and variables associated with disease severity such as age, motor manifestation, or the use of dopamine precursors or agonists.[3] Similarly, this study found no association between these variables and ^{3}H-imipramine–binding measures.

A peripheral marker for depression in PD would be useful because symptoms of depression and PD may overlap. When a B_{max} value was chosen to provide maximum correct classification of depression among patients with PD, the specificity and sensitivity of the measure were too low to be useful as a screen. Despite this, the decrease in B_{max} in depressed patients with PD and the correlation between CSF and platelet measures support a major alteration in serotonergic metabolism in PD that may explain some of the behavioral manifestations of PD.

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References

1. Mayeux R, Stern Y, Cote L, Williams JBW. Altered serotonin metabolism in depressed patients with Parkinson's disease. *Neurology.* 1984;34:642-646.
2. Mayeux R, Stern Y, Sano M, Williams JBW, Coté L. The relationship of serotonin to depression in Parkinson's disease. *Mov Disord.* 1988;3:237-244.
3. Mayeux R, Stern Y, Williams JBW. Clinical and biochemical features of depression in Parkinson's disease. *Am J Psychiatry.* 1986;143:756-759.
4. Kostic VS, Djuricic BM, Covickovic-Sternis N, Bumbasirevic L, Mrsulja BB. Depression and Parkinson's disease: possible role of serotonergic mechanisms. *J Neurol.* 1987;234:94-96.
5. Sano M, Stern Y, Williams JBW, et al. Coexisting dementia and depression in Parkinson's disease. *Arch Neurol.* 1989;46:1284-1286.
6. Van Praag HM. Depression. *Lancet.* 1982;2:1259-1264.
7. Van Praag HM, de Haan S. Central serotonin metabolism and frequency of depression. *Psychiatr Res.* 1979;1:219-224.
8. Langer SZ, Galzin AM, Poirier MF, et al. Association of the (^{3}H)-imipramine and (^{3}H)-paroxetine binding with the 5HT transporter in brain and platelets: relevance to studies in depression. *J Recept Res.* 1987;7:499-521.
9. Stanley M, Virgilio J, Gershon S. Tritiated imipramine binding sites are decreased in the frontal cortex of suicides. *Science.* 1982;216:1337-1338.
10. Meltzer HY. Platelet markers of suicidality. In: Mann JJ, Stanley M, eds. Psychobiology of suicidal behavior. *Ann N Y Acad Sci.* 1986;487:271-280.
11. Myerson L, Winogle LP, Able MS, et al. Human brain receptor alterations in suicide victims. *Pharmacol Biochem Behav.* 1982;17:159-163.
12. Arbilla S, Briley M, Cathala F, Langer SZ, Pornin C, Raisman R. Parallel changes in [^{3}H]-imipramine binding sites in cat brain and platelets following chronic treatment with imipramine. *Proc Biol Psychiatry Soc.* 1980;35:154-155.
13. Raisman R, Cash R, Agid Y. Parkinson's disease: decreased density of ^{3}H-imipramine and ^{3}H-paroxetine binding sites in putamen. *Neurology.* 1986;36:556-560.
14. Suranyi-Cadote BE, Gauthier S, Lafaille F. Platelet ^{3}H-imipramine binding distinguishes depression from Alzheimer dementia. *Life Sci.* 1985;37:2305-2311.
15. Schneider LS, Chui HC, Severson JA, Sloane RB. Decreased platelet binding in Parkinson's disease. *Biol Psychiatry.* 1988;24:348-351.
16. Stern MB. The clinical characteristics of Parkinson's disease and parkinsonian syndromes: diagnosis and assessment. In: Stern M, Hurtig H, eds. *The Comprehensive Management of Parkinson's Disease.* New York, NY: PMA; 1988:3-50.
17. Schwab JF, England AC. Projection technique for evaluating surgery in Parkinson's disease. In: Gillingham FJ, Donaldson IML, eds. *Third Symposium on Parkinson's Disease.* Edinburgh, Scotland: E & S Livingstone; 1969:152-157.
18. Hoehn MM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;17:427-442.
19. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of the patient for the clinician. *J Psychiatr Res.* 1975;12:189-198.
20. Stern Y, Sano M, Paulson J. Modified Mini-Mental State examination: validity and reliability. *Neurology.* 1986;37:179. Abstract.
21. Williams JBW. A structured interview guide for the Hamilton Depression Rating Scale. *Arch Gen Psychiatry.* 1988;45:742-747.
22. Briley MS, Langer R, Raisman S. Tritiated imipramine binding sites are decreased in platelets of untreated depressed patients. *Science.* 1980;209:303-307.
23. Asarch KB, Shih JC, Kulcsar A. Decreased ^{3}H-imipramine binding in depressed males and females. *Commun Psychopharm.* 1980;4:425-432.
24. American Psychiatric Association, Committee on Nomenclature and Statistics. *Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition.* Washington, DC: American Psychiatric Association; 1987:218-232.
25. Spitzer RL, Williams JBW, Gibbon M, First MB. *Structured Clinical Interview for DSM-III-R.* New York, NY: Biometrics Research Department, New York State Psychiatric Institute; 1988.
26. Scatchard G. The attraction of proteins for small molecules and ions. *Ann N Y Acad Sci.* 1949;51:660-672.
27. Fleiss JL. *Statistical Methods for Rates and Proportions.* 2nd ed. New York, NY: John Wiley & Sons Inc; 1981:1-18.
28. Stanley M, Traskman-Bendz L, Dorovini-Zis K. Correlations between aminergic metabolites simultaneously obtained from human CSF and brain. *Life Sci.* 1985;37:1279-1286.
29. Mayberg HS, Starkstein SE, Sadzot B, et al. Selective hypometabolism in the inferior frontal lobe of depressed patients with Parkinson's disease. *Ann Neurol.* 1990;26:57-64.
30. Sano M, Stern Y, Coté L, Williams JBW. Depression in Parkinson's disease: a biochemical model. *J Neuropsychiatry Clin Neurosci.* 1990;2:88-91.
31. Jellinger K. Overview of morphological changes in Parkinson's disease. In: Yahr MD, Bergmann KJ, eds. *Advances in Neurology: Parkinson's Disease.* New York, NY: Raven Press; 1986:1-19.

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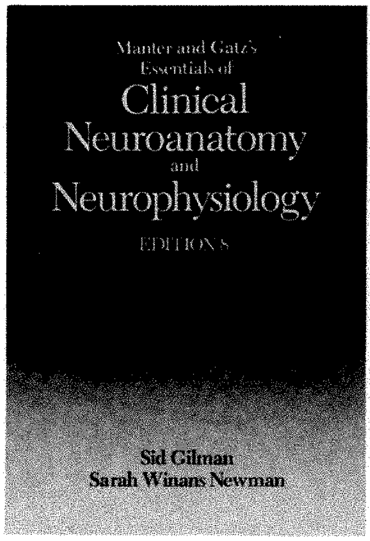

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TABLE OF CONTENTS

I. Basic Principles
1. Introduction to the Nervous System. 2. The Physiology of Nerve Cells.

II. The Peripheral Nervous System
3. The Spinal Nerves. 4. Spinal Reflexes and Muscle Tone. 5. The Autonomic Nervous System.

III. Ascending and Descending Pathways
6. Pain and Temperature. 7. Proprioception and Tactile Discrimination. 8. Touch. 9. The Descending Pathways. 10. Lesions of the Peripheral Nerves, Spinal Roots, and Spinal Cord.

IV. Brain Stem and Cerebellum
11. Anatomy of the Brain Stem: Medulla, Pons, and Midbrain Medulla. 12. The Cranial Nerves. 13. Cranial Nerves of the Medulla. 14. Cranial Nerves of the Pons and Midbrain. 15. Lesions of the Brain Stem. 16. Hearing. 17. The Vestibular System. 18. The Cerebellum.

V. Higher Levels of the Nervous System
19. The Basal Ganglia and Related Structures. 20. Vision. 21. Optic Reflexes. 22. The Thalamus. 23. The Hypothalamus and Limbic System. 24. The Rhinencephalon and Olfactory Reflexes. 25. The Cerebral Cortex. 26. Chemical Neuroanatomy.

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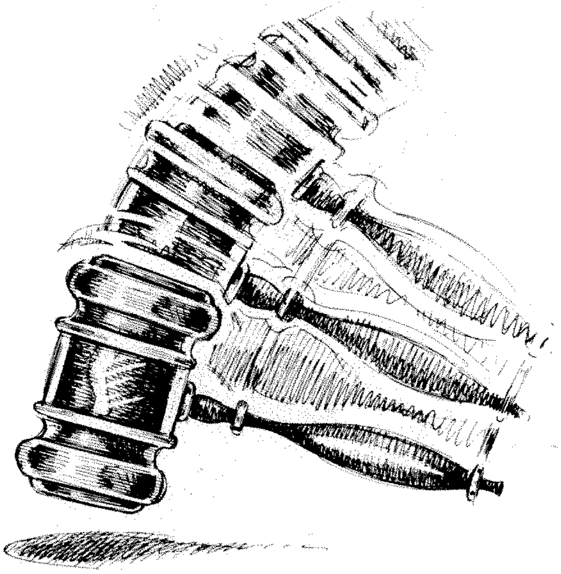

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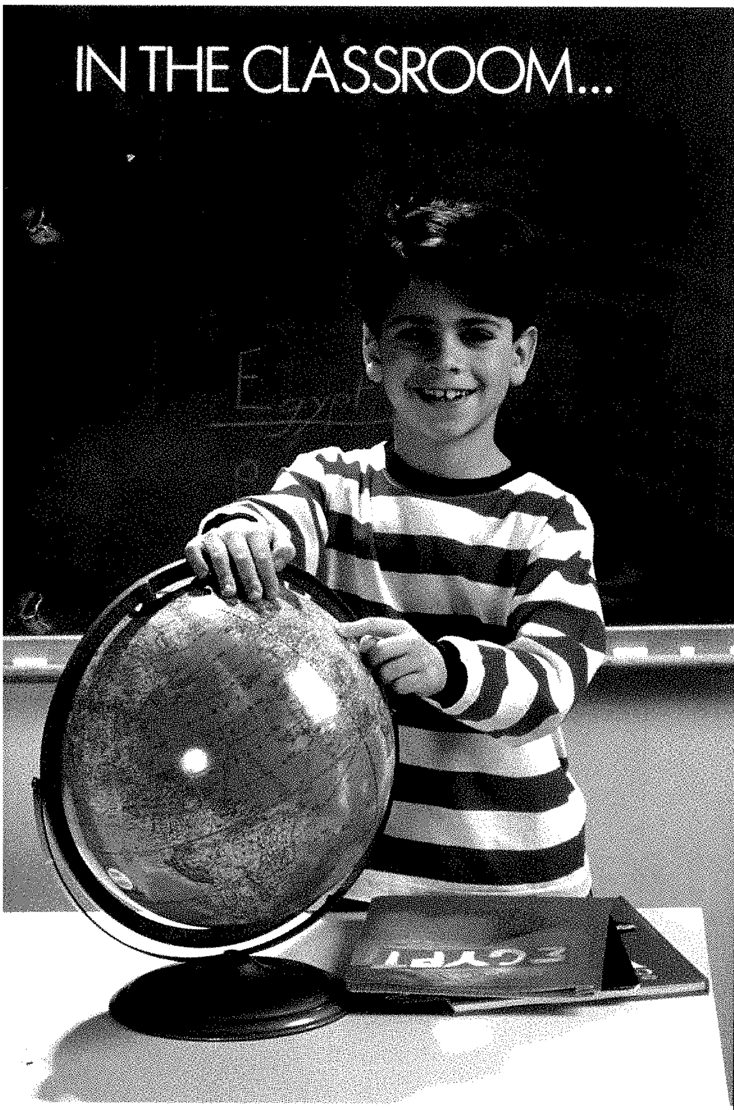

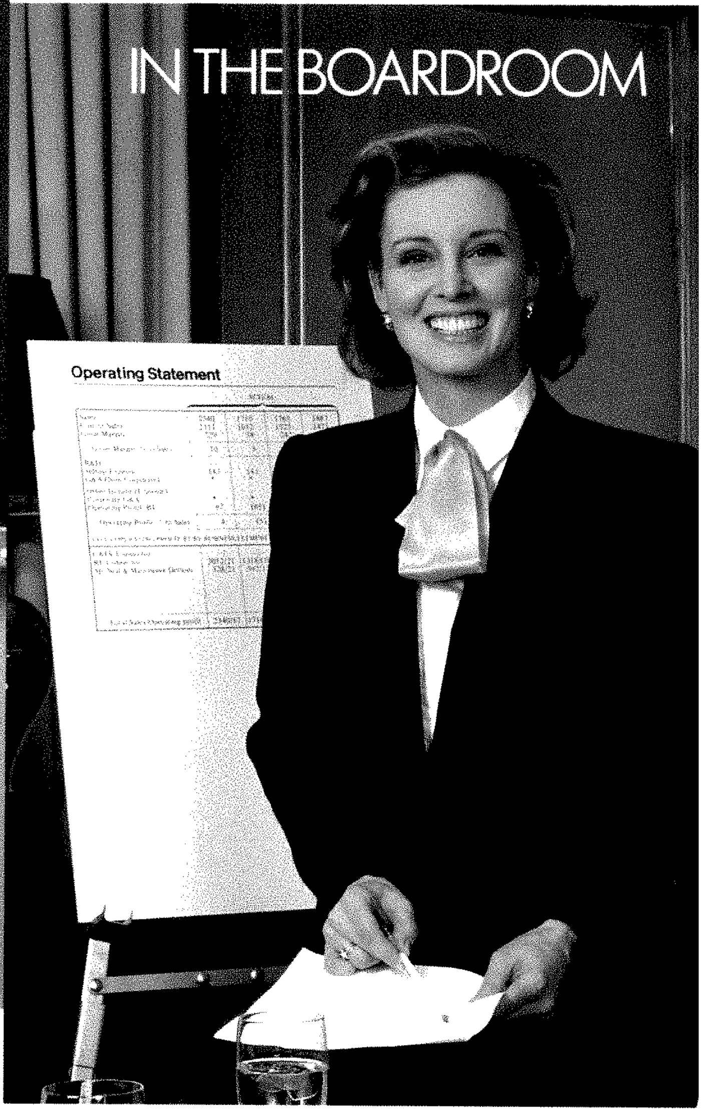

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References:

1. Smith DB, Mattson RH, Cramer JA et al. Results of a nationwide Veterans Administration cooperative study comparing the efficacy and toxicity of carbamazepine, phenobarbital, phenytoin, and primidone. *Epilepsia*. 1987;28(suppl 3):S50-S58.
2. Mattson RH, Cramer JA, Collins JF et al. Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily generalized tonic-clonic seizures. *N Engl J Med*. 1985;313:145-151.
3. Herranz JL, Armijo JA, Arteaga R. Clinical side effects of phenobarbital, primidone, phenytoin, carbamazepine, and valproate during monotherapy in children. *Epilepsia*. 1988;29:794-804.

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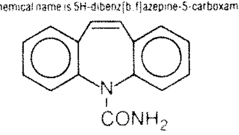
>
> ALTHOUGH REPORTS OF TRANSIENT OR PERSISTENT DECREASED PLATELET OR WHITE BLOOD CELL COUNTS ARE NOT UNCOMMON IN ASSOCIATION WITH THE USE OF TEGRETOL, DATA ARE NOT AVAILABLE TO ESTIMATE ACCURATELY THEIR INCIDENCE OR OUTCOME. HOWEVER, THE VAST MAJORITY OF THE CASES OF LEUKOPENIA HAVE NOT PROGRESSED TO THE MORE SERIOUS CONDITIONS OF APLASTIC ANEMIA OR AGRANULOCYTOSIS.
>
> BECAUSE OF THE VERY LOW INCIDENCE OF AGRANULOCYTOSIS AND APLASTIC ANEMIA, THE VAST MAJORITY OF MINOR HEMATOLOGIC CHANGES OBSERVED IN MONITORING OF PATIENTS ON TEGRETOL ARE UNLIKELY TO SIGNAL THE OCCURRENCE OF EITHER ABNORMALITY. NONETHELESS, COMPLETE PRETREATMENT HEMATOLOGICAL TESTING SHOULD BE OBTAINED AS A BASELINE. IF A PATIENT IN THE COURSE OF TREATMENT EXHIBITS LOW OR DECREASED WHITE BLOOD CELL OR PLATELET COUNTS, THE PATIENT SHOULD BE MONITORED CLOSELY. DISCONTINUATION OF THE DRUG SHOULD BE CONSIDERED IF ANY EVIDENCE OF SIGNIFICANT BONE MARROW DEPRESSION DEVELOPS.

Before prescribing Tegretol, the physician should be thoroughly familiar with the details of this prescribing information, particularly regarding use with other drugs, especially those which accentuate toxicity potential.

DESCRIPTION

Tegretol, carbamazepine USP, is an anticonvulsant and specific analgesic for trigeminal neuralgia, available as chewable tablets of 100 mg and tablets of 200 mg for oral administration. Its chemical name is 5H-dibenz[b,f]azepine-5-carboxamide, and its structural formula is



Carbamazepine USP is a white to off-white powder, practically insoluble in water and soluble in alcohol and in acetone. Its molecular weight is 236.27.

Inactive Ingredients. Colloidal silicon dioxide, FD&C Red No. 3 (chewable tablets only), FD&C Red No. 40 (200-mg tablets only), flavoring (chewable tablets only), gelatin, glycerin, magnesium stearate, sodium starch glycolate (chewable tablets only), starch, stearic acid, and sucrose (chewable tablets only).

CLINICAL PHARMACOLOGY

In controlled clinical trials, Tegretol has been shown to be effective in the treatment of psychomotor and grand mal seizures, as well as trigeminal neuralgia.

It has demonstrated anticonvulsant properties in rats and mice with electrically and chemically induced seizures. It appears to act by reducing polysynaptic responses and blocking the posttetanic potentiation. Tegretol greatly reduces or abolishes pain induced by stimulation of the infraorbital nerve in cats and rats. It depresses thalamic potential and bulbar and polysynaptic reflexes, including the linguomandibular reflex in cats. Tegretol is chemically unrelated to other anticonvulsants or other drugs used to control the pain of trigeminal neuralgia. The mechanism of action remains unknown.

Tegretol tablets are adequately absorbed after oral administration at a slower rate than a solution, thus avoiding undesirably high peak concentrations. Tegretol chewable tablets may produce higher peak levels than the same dose given as regular tablets. Tegretol in blood is 76% bound to plasma proteins. Plasma levels of Tegretol are variable and may range from 0.5-25 μg/ml, with no apparent relationship to the daily intake of the drug. Usual adult therapeutic levels are between 4 and 12 μg/ml. Following oral administration, serum levels peak at 4 to 5 hours. The CSF/serum ratio is 0.22, similar to the 22% unbound Tegretol in serum. Because Tegretol may induce its own metabolism, the half-life is also variable. Initial half-life values range from 25-65 hours, with 12-17 hours on repeated doses. Tegretol is metabolized in the liver. After oral administration of 14C-carbamazepine, 72% of the administered radioactivity was found in the urine and 28% in the feces. This urinary radioactivity was composed largely of hydroxylated and conjugated metabolites, with only 3% of unchanged Tegretol. Transplacental passage of Tegretol is rapid (30 to 60 minutes), and the drug is accumulated in fetal tissues, with higher levels found in liver and kidney than in brain and lungs.

INDICATIONS AND USAGE

Epilepsy: Tegretol is indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Tegretol as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types:

1. Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types.
2. Generalized tonic-clonic seizures (grand mal).
3. Mixed seizure patterns which include the above, or other partial or generalized seizures.

Absence seizures (petit mal) do not appear to be controlled by Tegretol (see PRECAUTIONS, General).

Trigeminal Neuralgia: Tegretol is indicated in the treatment of the pain associated with true trigeminal neuralgia.

Beneficial results have also been reported in glossopharyngeal neuralgia.

This drug is not a simple analgesic and should not be used for the relief of trivial aches or pains.

CONTRAINDICATIONS

Tegretol should not be used in patients with a history of previous bone marrow depression, hypersensitivity to the drug, or known sensitivity to any of the tricyclic compounds, such as amitriptyline, desipramine, imipramine, protriptyline, nortriptyline, etc. Likewise, on theoretical grounds its use with monoamine oxidase inhibitors is not recommended. Before administration of Tegretol, MAO inhibitors should be discontinued for a minimum of fourteen days, or longer if the clinical situation permits.

WARNINGS

Patients with a history of adverse hematologic reaction to any drug may be particularly at risk.

Severe dermatologic reactions including toxic epidermal necrolysis (Lyell's syndrome) and Stevens-Johnson syndrome, have been reported with Tegretol. These reactions have been extremely rare. However, a few fatalities have been reported.

Tegretol has shown mild anticholinergic activity; therefore, patients with increased intraocular pressure should be closely observed during therapy.

Because of the relationship of the drug to other tricyclic compounds, the possibility of activation of a latent psychosis and, in elderly patients, of confusion or agitation should be borne in mind.

PRECAUTIONS

General: Before initiating therapy, a detailed history and physical examination should be made.

Tegretol should be used with caution in patients with a mixed seizure disorder that includes atypical absence seizures, since in these patients Tegretol has been associated with increased frequency of generalized convulsions (see INDICATIONS AND USAGE).

Therapy should be prescribed only after critical benefit-to-risk appraisal in patients with a history of cardiac, hepatic or renal damage, adverse hematologic reaction to other drugs, or interrupted courses of therapy with Tegretol.

Information for Patients: Patients should be made aware of the early toxic signs and symptoms of a potential hematologic problem, such as fever, sore throat, ulcers in the mouth, easy bruising, petechial or purpuric hemorrhage, and should be advised to report to the physician immediately if any such signs or symptoms appear.

Since dizziness and drowsiness may occur, patients should be cautioned about the hazards of operating machinery or automobiles or engaging in other potentially dangerous tasks.

Laboratory Tests: Complete pretreatment blood counts, including platelets and possibly reticulocytes and serum iron, should be obtained as a baseline. If a patient in the course of treatment exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely. Discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.

Baseline and periodic evaluations of liver function, particularly in patients with a history of liver disease, must be performed during treatment with this drug since liver damage may occur. The drug should be discontinued immediately in cases of aggravated liver dysfunction or active liver disease.

Baseline and periodic eye examinations, including slit-lamp, funduscopy and tonometry, are recommended since many phenothiazines and related drugs have been shown to cause eye changes.

Baseline and periodic complete urinalysis and BUN determinations are recommended for patients treated with this agent because of observed renal dysfunction.

Monitoring of blood levels (see CLINICAL PHARMACOLOGY) has increased the efficacy and safety of anticonvulsants. This monitoring may be particularly useful in cases of dramatic increase in seizure frequency and for verification of compliance. In addition, measurement of drug serum levels may aid in determining the cause of toxicity when more than one medication is being used.

Thyroid function tests have been reported to show decreased values with Tegretol administered alone.

Hyponatremia has been reported in association with Tegretol use, either alone or in combination with other drugs.

Drug Interactions: The simultaneous administration of phenobarbital, phenytoin, or primidone, or a combination of two, produces a marked lowering of serum levels of Tegretol. The effect of valproic acid on Tegretol blood levels is not clearly established, although an increase in the ratio of active 10, 11-epoxide metabolite to parent compound is a consistent finding.

The half-lives of phenytoin, warfarin, doxycycline, and theophylline were significantly shortened when administered concurrently with Tegretol. Haloperidol and valproic acid serum levels may be reduced when these drugs are administered with Tegretol. The doses of these drugs may therefore have to be increased when Tegretol is added to the therapeutic regimen.

Concomitant administration of Tegretol with erythromycin, cimetidine, propoxyphene, isoniazid, fluoxetine or calcium channel blockers has been reported to result in elevated plasma levels of carbamazepine resulting in toxicity in some cases. Also, concomitant administration of carbamazepine and lithium may increase the risk of neurotoxic side effects.

Alterations of thyroid function have been reported in combination therapy with other anticonvulsant medications.

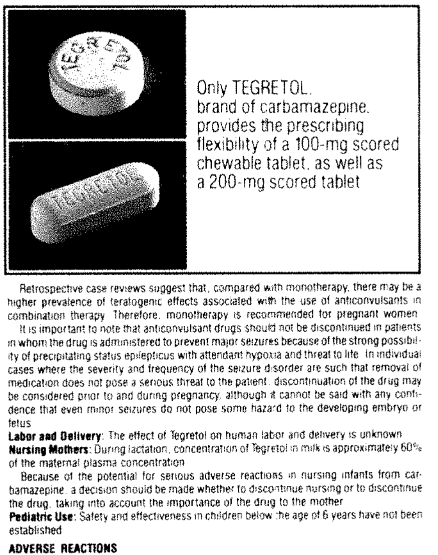
Breakthrough bleeding has been reported among patients receiving concomitant oral contraceptives and their reliability may be adversely affected.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Carbamazepine, when administered to Sprague-Dawley rats for two years in the diet at doses of 25, 75, and 250 mg/kg/day, resulted in a dose-related increase in the incidence of hepatocellular tumors in females and of benign interstitial cell adenomas in the testes of males.

Carbamazepine must, therefore, be considered to be carcinogenic in Sprague-Dawley rats. Bacterial and mammalian mutagenicity studies using carbamazepine produced negative results. The significance of these findings relative to the use of carbamazepine in humans is, at present, unknown.

Pregnancy Category C: Tegretol has been shown to have adverse effects in reproduction studies in rats when given orally in dosages 10-25 times the maximum human daily dosage of 1200 mg. In rat teratology studies, 2 of 135 offspring showed kinked ribs at 250 mg/kg and 4 of 119 offspring at 650 mg/kg showed other anomalies (cleft palate, 1; talipes, 1; anophthalmos, 2). In reproduction studies in rats, nursing offspring demonstrated a lack of weight gain and an unkempt appearance at a maternal dosage level of 200 mg/kg.

There are no adequate and well-controlled studies in pregnant women. Epidemiological data suggest that there may be an association between the use of carbamazepine during pregnancy and congenital malformations, including spina bifida. Tegretol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.



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Retrospective case reviews suggest that, compared with monotherapy, there may be a higher prevalence of teratogenic effects associated with the use of anticonvulsants in combination therapy. Therefore, monotherapy is recommended for pregnant women.

It is important to note that anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus.

Labor and Delivery: The effect of Tegretol on human labor and delivery is unknown.

Nursing Mothers: During lactation, concentration of Tegretol in milk is approximately 60% of the maternal plasma concentration.

Because of the potential for serious adverse reactions in nursing infants from carbamazepine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 6 years have not been established.

ADVERSE REACTIONS

If adverse reactions are of such severity that the drug must be discontinued, the physician must be aware that abrupt discontinuation of any anticonvulsant drug in a responsive epileptic patient may lead to seizures or even status epilepticus with its life-threatening hazards.

The most severe adverse reactions have been observed in the hemopoietic system (see boxed WARNING), the skin and the cardiovascular system.

The most frequently observed adverse reactions, particularly during the initial phases of therapy, are dizziness, drowsiness, unsteadiness, nausea, and vomiting. To minimize the possibility of such reactions, therapy should be initiated at the low dosage recommended.

The following additional adverse reactions have been reported:

Hemopoietic System. Aplastic anemia, agranulocytosis, pancytopenia, bone marrow depression, thrombocytopenia, leukopenia, leukocytosis, eosinophilia, acute intermittent porphyria.

Skin: Pruritic and erythematous rashes, urticaria, toxic epidermal necrolysis (Lyell's syndrome) (see WARNINGS), Stevens-Johnson syndrome (see WARNINGS), photosensitivity reactions, alterations in skin pigmentation, exfoliative dermatitis, erythema multiforme and nodosum, purpura, aggravation of disseminated lupus erythematosus, alopecia, and diaphoresis. In certain cases, discontinuation of therapy may be necessary. Isolated cases of hirsutism have been reported, but a causal relationship is not clear.

Cardiovascular System. Congestive heart failure, edema, aggravation of hypertension, hypotension, syncope and collapse, aggravation of coronary artery disease, arrhythmias and AV block, primary thrombophlebitis, recurrence of thrombophlebitis, and adenopathy or lymphadenopathy.

Some of these cardiovascular complications have resulted in fatalities. Myocardial infarction has been associated with other tricyclic compounds.

Liver: Abnormalities in liver function tests, cholestatic and hepatocellular jaundice, hepatitis.

Respiratory System. Pulmonary hypersensitivity characterized by fever, dyspnea, pneumonitis or pneumonia.

Genitourinary System. Urinary frequency, acute urinary retention, oliguria with elevated blood pressure, azotemia, renal failure, and impotence. Albuminuria, glycosuria, elevated BUN and microscopic deposits in the urine have also been reported.

Testicular atrophy occurred in rats receiving Tegretol orally from 4 to 52 weeks at dosage levels of 50 to 400 mg/kg/day. Additionally, rats receiving Tegretol in the diet for two years at dosage levels of 25, 75, and 250 mg/kg/day had a dose-related incidence of testicular atrophy and aspermatogenesis. In dogs, it produced a brownish discoloration, presumably a metabolite, in the urinary bladder at dosage levels of 50 mg/kg and higher. Relevance of these findings to humans is unknown.

Nervous System. Dizziness, drowsiness, disturbances of coordination, confusion, headache, fatigue, blurred vision, visual hallucinations, transient diplopia, oculomotor disturbances, nystagmus, speech disturbances, abnormal involuntary movements, peripheral neuritis and paresthesias, depression with agitation, talkativeness, tinnitus, and hyperacusis.

There have been reports of associated paralysis and other symptoms of cerebral arterial insufficiency, but the exact relationship of these reactions to the drug has not been established.

Digestive System: Nausea, vomiting, gastric distress and abdominal pain, diarrhea, constipation, anorexia, and dryness of the mouth and pharynx, including glossitis and stomatitis.

Eyes. Scattered, punctate, cortical lens opacities, as well as conjunctivitis, have been reported. Although a direct causal relationship has not been established, many phenothiazines and related drugs have been shown to cause eye changes.

Musculoskeletal System. Aching joints and muscles, and leg cramps.

Metabolism. Fever and chills. Inappropriate antidiuretic hormone (ADH) secretion syndrome has been reported. Cases of frank water intoxication, with decreased serum sodium (hyponatremia) and confusion, have been reported in association with Tegretol use (see PRECAUTIONS, Laboratory Tests).

Other. Isolated cases of a lupus erythematosus-like syndrome have been reported. There have been occasional reports of elevated levels of cholesterol, HDL cholesterol and triglycerides in patients taking anticonvulsants.

A case of aseptic meningitis, accompanied by myoclonus and peripheral eosinophilia, has been reported in a patient taking carbamazepine in combination with other medications. The patient was successfully dechallenged, and the meningitis reappeared upon rechallenge with carbamazepine.

DRUG ABUSE AND DEPENDENCE

No evidence of abuse potential has been associated with Tegretol, nor is there evidence of psychological or physical dependence in humans.

OVERDOSAGE

Acute Toxicity

Lowest known lethal dose: adults, >60 g (39-year-old man). Highest known doses survived: adults, 30 g (31-year-old woman); children, 10 g (6-year-old boy); small children, 5 g (3-year-old girl).

Oral LD 50 in animals (mg/kg): mice, 1100-3750; rats, 3850-4025; rabbits, 1500-2680; guinea pigs, 920.

Signs and Symptoms

The first signs and symptoms appear after 1-3 hours. Neuromuscular disturbances are the most prominent. Cardiovascular disorders are generally milder, and severe cardiac complications occur only when very high doses (>60 g) have been ingested.

Respiration. Irregular breathing, respiratory depression.

Cardiovascular System. Tachycardia, hypotension or hypertension, shock, conduction disorders.

Nervous System and Muscles. Impairment of consciousness ranging in severity to deep coma. Convulsions, especially in small children. Motor restlessness, muscular twitching, tremor, athetoid movements, opisthotonos, ataxia, drowsiness, dizziness, mydriasis, nystagmus, adiadochokinesia, ballism, psychomotor disturbances, dysmetria. Initial hyperreflexia, followed by hyporeflexia.

Gastrointestinal Tract. Nausea, vomiting.

Kidneys and Bladder. Anuria or oliguria, urinary retention.

Laboratory Findings. Isolated instances of overdosage have included leukocytosis, reduced leukocyte count, glycosuria and acetonuria. EEG may show dysrhythmias.

Combined Poisoning: When alcohol, tricyclic antidepressants, barbiturates or hydantoins are taken at the same time, the signs and symptoms of acute poisoning with Tegretol may be aggravated or modified.

Treatment

The prognosis in cases of severe poisoning is critically dependent upon prompt elimination of the drug, which may be achieved by inducing vomiting, irrigating the stomach, and by taking appropriate steps to diminish absorption. If these measures cannot be implemented without risk on the spot, the patient should be transferred at once to a hospital, while ensuring that vital functions are safeguarded. There is no specific antidote.

Elimination of the Drug. Induction of vomiting.

Gastric lavage. Even when more than 4 hours have elapsed following ingestion of the drug, the stomach should be repeatedly irrigated, especially if the patient has also consumed alcohol.

Measures to Reduce Absorption. Activated charcoal, laxatives.

Measures to Accelerate Elimination. Forced diuresis.

Dialysis is indicated only in severe poisoning associated with renal failure. Replacement transfusion is indicated in severe poisoning in small children.

Respiratory Depression. Keep the airways free; resort, if necessary, to endotracheal intubation, artificial respiration, and administration of oxygen.

Hypotension, Shock: Keep the patient's legs raised and administer a plasma expander. If blood pressure fails to rise despite measures taken to increase plasma volume, use of vasoactive substances should be considered.

Convulsions. Diazepam or barbiturates.

Warning. Diazepam or barbiturates may aggravate respiratory depression (especially in children), hypotension, and coma. However, barbiturates should not be used if drugs that inhibit monoamine oxidase have also been taken by the patient either in overdosage or in recent therapy (within one week).

Surveillance. Respiration, cardiac function (ECG monitoring), blood pressure, body temperature, pupillary reflexes, and kidney and bladder function should be monitored for several days.

Treatment of Blood Count Abnormalities. If evidence of significant bone marrow depression develops, the following recommendations are suggested: (1) stop the drug, (2) perform daily CBC, platelet and reticulocyte counts, (3) do a bone marrow aspiration and trephine biopsy immediately and repeat with sufficient frequency to monitor recovery.

Special periodic studies might be helpful as follows: (1) white cell and platelet antibodies, (2) 59Fe—ferrokinetic studies, (3) peripheral blood cell typing, (4) cytogenetic studies on marrow and peripheral blood, (5) bone marrow culture studies for colony-forming units, (6) hemoglobin electrophoresis for A_2 and F hemoglobin, and (7) serum folic acid and B_{12} levels.

A fully developed aplastic anemia will require appropriate, intensive monitoring and therapy, for which specialized consultation should be sought.

DOSAGE AND ADMINISTRATION

Monitoring of blood levels has increased the efficacy and safety of anticonvulsants (see PRECAUTIONS, Laboratory Tests). Dosage should be adjusted to the needs of the individual patient. A low initial daily dosage with a gradual increase is advised. As soon as adequate control is achieved, the dosage may be reduced very gradually to the minimum effective level. Tablets should be taken with meals.

Epilepsy (see INDICATIONS AND USAGE)

Adults and children over 12 years of age—Initial: 200 mg b.i.d. Increase at weekly intervals by adding up to 200 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg daily in children 12 to 15 years of age, and 1200 mg daily in patients above 15 years of age. Doses up to 1600 mg daily have been used in adults in rare instances. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 800-1200 mg daily.

Children 6-12 years of age—Initial: 100 mg b.i.d. Increase at weekly intervals by adding 100 mg per day using a t.i.d. or q.i.d. regimen until the best response is obtained. Dosage should generally not exceed 1000 mg. ***Maintenance:*** Adjust dosage to the minimum effective level, usually 400-800 mg daily.

Combination Therapy: Tegretol may be used alone or with other anticonvulsants. When added to existing anticonvulsant therapy, the drug should be added gradually while the other anticonvulsants are maintained or gradually decreased, except phenytoin, which may have to be increased (see PRECAUTIONS, Drug Interactions and Pregnancy Category C).

Trigeminal Neuralgia (see INDICATIONS AND USAGE)

Initial: 100 mg b.i.d. on the first day for a total daily dose of 200 mg. This daily dose may be increased by up to 200 mg a day using increments of 100 mg every 12 hours only as needed to achieve freedom from pain. Do not exceed 1200 mg daily.

Maintenance: Control of pain can be maintained in most patients with 400 mg to 800 mg daily. However, some patients may be maintained on as little as 200 mg daily, while others may require as much as 1200 mg daily. At least once every 3 months throughout the treatment period, attempts should be made to reduce the dose to the minimum effective level or even to discontinue the drug.

HOW SUPPLIED

Chewable Tablets 100 mg—round, red-speckled, pink, single-scored (imprinted Tegretol on one side and 52 twice on the scored side)

Bottles of 100	NDC 58887-052-30
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 58887-052-32

Tablets 200 mg—capsule-shaped, pink, single-scored (imprinted Tegretol on one side and 27 twice on the scored side)

Bottles of 100	NDC 58887-027-30
Bottles of 1000	NDC 58887-027-40
Unit Dose (blister pack)	
Box of 100	
(strips of 10)	NDC 58887-027-32

Samples, when available, are identified by the word *SAMPLE* appearing on each tablet.

Protect from moisture.

Dispense in tight container (USP).

Also available as: Tegretol suspension 100 mg/5 ml, in 450 ml bottles.

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Ultrasound Findings in Spontaneous Carotid Artery Dissection

The Value of Duplex Sonography

Matthias Sturzenegger, MD

• Extracranial and transcranial Doppler and duplex sonographic findings in six patients with internal carotid artery dissection proven by angiography is reported. Extracranial Doppler analysis showed occlusion without a recordable signal from the internal carotid artery at any level or stenosis with accelerated flow in the high cervical segment. Transcranial Doppler findings demonstrated the hemodynamic consequences of the internal carotid artery occlusion or stenosis with collateral flow across the circle of Willis and also showed the dampened pulse wave of the middle cerebral artery ipsilateral to the dissection. In duplex sonography, the indirect signs indicating internal carotid artery dissection were a patent carotid bifurcation and proximal internal carotid artery segment but with no or only a short systolic flow signal. Atherosclerotic wall changes were absent, an important finding that suggests nonatherosclerotic stenosis or occlusion. Direct signs making the diagnosis likely were a tapering of the internal carotid artery lumen distal to the bulb, an irregular membrane crossing the vessel lumen, and the demonstration of a true lumen with flow and a false one without flow. While cerebral angiography is still considered the gold standard, ultrasound may become the primary modality for early diagnosis. Doppler and duplex examinations help to indicate angiography and are the methods of choice for follow-up investigations. They clearly demonstrate spontaneous recanalization with normalization of carotid circulation or, in case of persistent occlusion, improvement of collateral blood supply. Sequential examinations may prove helpful to determine the duration of anticoagulant treatment.

(*Arch Neurol.* 1991;48:1057-1063)

The cervical part of the internal carotid artery (ICA) is by far the most frequent site of spontaneous wall dissection,[1-3] but any brain-supplying artery may be affected.[4] The exact frequency is unknown, but it may be quite underestimated. With less rigid indications for cerebral angiography[5-7] in the last few years, an increasing number of patients with spontaneous dissection of the ICA (ICD) have been identified.[8] From this experience, we have learned that the clinical presentation of ICD may be extremely variable, ranging from the patient with unspecific headache or even no clinical symptoms and signs to the patient with severe stroke and rapidly ensuing death. These clinical extremes usually do not give rise to further investigations, and the real cause, ICD, goes unrecognized.

Younger patients are preferentially affected: Hart and Miller[9] found two cases (2%) among 100 patients with stroke under the age of 40 years, and Bogousslavsky and Regli[10] found nine cases (22%) among 41 patients with stroke under the age of 30 years. Mean age at presentation in a group of 146 cases[2] was 45 years; 70% were between 35 and 50 years old. The younger age at presentation is suggestive of ICD rather than atherosclerotic carotid disease.[2,4] Considering all patients with stroke, ICD is a rare cause of stroke: among a series of 1200 consecutive patients with stroke,[11] 30 (2.5%) had ICD. In another series of 4531 patients examined with cerebral angiography because of acute cerebrovascular symptoms,[12] extracranial carotid artery dissection was diagnosed in 11 (0.24%).

When the characteristic triad of facial or neck pain, ipsilateral oculosympathetic paresis, and hemispheric ischemic symptoms is present, diagnosis may be strongly suspected on clinical grounds.[2,4,13-16] For definite diagnosis, angiography is required, which can show characteristic but also variable signs.[3,4,17-21] The findings, except double lumen, are nonspecific. Differential diagnosis includes arterial compression or invasion by tumor or pharyngeal inflammation, congenital hypoplasia, vasculitis, radiation-induced arteriopathy, and vasospasm.

In general, prognosis is good, and spontaneous recanalization occurs in more than 80% of patients.[2,4] However, persisting disability can result,[21,22] owing to ensuing stroke. Considering patients with ICD and stroke,[11] prognosis is clearly worse: recanalization occurs in only 60% and death in 23%, and 48% of the patients remain severely disabled. Stroke is, as known from angiography,[18,23] mostly due to embolism from local thrombosis at the site of dissection. Rarely, insufficient collateral blood supply causes hemodynamic infarction.

Because of the danger of embolism, early anticoagulation is considered the treatment of choice. However, its effectiveness has not been proved yet by a randomized controlled study. On the other hand, to my knowledge there is no case of ICD reported in the literature in which symptoms worsened with antico-

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Table 1.—Clinical Findings*

Patient No./ Age, y/Sex	Symptoms	Signs	Vascular Risk Factors	Treatment	Evolution
1/49/M	Recurrent TIA (L hemiparesis), pain R eye and temple	None	Migraine, hypertension, smoking, cholesterol	Heparin sodium, coumarin	Resolution after 12 d
2/42/F	R hemiparesis, aphasia, occipital headache	R hemiparesis	Migraine, hypertension	Heparin, coumarin	Partial recanalization with persisting slight stenosis after 15 wk
3/41/M	Recurrent R amaurosis fugax, recurrent TIA (R hemiparesis), pain R temple and cheek	Loss of consciousness, R hemiparesis, transient aphasia, bruit R carotid	None	Aspirin	Resolution on both sides after 2 mo
4/41/M	R hemiparesis, aphasia, frontal headache	R hemiparesis	None	Heparin, coumarin	Persisting occlusion after 2 mo, better intracranial collateral flow
5/40/M	Recurrent TIA (L hemiparesis), gait disturbance, pain R eye and temple	Partial HS on R, hemianopia to L, L hemiparesis, L sensory neglect, CT: infarction	Migraine, hypertension	Heparin, coumarin	Symmetric BFV in both MCAs after 5 d, complete recanalization after 6 wk
6/41/M	Recurrent TIA (asphasia), pain L eye and forehead	Partial HS, none on L	None	Heparin, coumarin	Resolution after 10 wk

*TIA indicates transient ischemic attack; HS, Horner's syndrome; CT, computed tomography; BFV, blood flow velocity; and MCA, middle cerebral artery.

agulant therapy. If anticoagulation is beneficial, early diagnosis is essential for the treatment of patients with ICD, a goal that can be achieved with combined ultrasonographic examination (CUE) using conventional extracranial direct and indirect Doppler sonography, transcranial Doppler sonography (TCD), and duplex scanning. I report my experience using CUE in six patients with ICD in the extracranial segment verified by angiography.

PATIENTS AND METHODS

Duplex Examination

A high-resolution, real-time, duplex ultrasound system (Diasonics SPA 1000, Sonotron Holding AG, Zug, Switzerland) was used that consisted of a 10-MHz echotomography imaging probe and a 4.5-MHz pulsed-wave Doppler probe with real-time gray-scale Fast-Fourier transform Doppler spectrum analysis. Common carotid artery (CCA), bulb, ICA, external carotid artery (ECA), and vertebral arteries were imaged on both sides.

Extracranial Doppler Examination

The technique for extracranial direct and indirect Doppler sonographic examination has been described in detail previously.[24] I used the same device as for TCD recordings, which is described below. The CCA, ECA, ICA, subclavian artery, and vertebral artery at the atlas were examined by continuous insonnation on both sides. Supratrochlear and ophthalmic arteries (OpAs), as well as carotid siphons, were measured by a transorbital approach.

TCD Examination

The technique for TCD recordings has been described in detail previously.[25-28] A microprocessor-controlled directional pulsed Doppler device operating at 2 MHz was used for all TCD ultrasound examinations (TC2-64, Eden Medizinische Elektronic GmbH, Ueberlingen, Germany). The middle cerebral artery (MCA), anterior cerebral artery, posterior cerebral artery, and ICA bifurcation were analyzed at different depths by a transtemporal approach and the intracranial vertebral and basilar arteries were analyzed through the occipital foramen. Systolic, diastolic, and mean blood flow velocity (BFV) were measured in each vessel. Pulsatility index (PI) was calculated according to the following formula: PI = (systolic BFV − diastolic BFV)/mean BFV.[25] The values of 52 normal controls served as reference. The MCA-BFV and PI values of the six patients were compared with those of the controls.

Cerebral Angiography

Selective CCA angiograms were obtained in all patients. Catheterizations were performed by the percutaneous femoral approach. In one case (case 3), direct CCA puncture was performed. Six French polyethylene catheters and a nonionic, low-osmolar contrast agent were used.

Statistical analysis was performed using simple regression analysis and the unpaired and paired t test.

RESULTS

Six patients (five men and one woman with a mean age of 42.5 years [range, 40 to 49 years]) admitted within a year with angiographically proved ICD were analyzed. Five had unilateral dissection and one (case 3) had bilateral dissection. The clinical findings are summarized in Table 1. Lower cranial nerve palsy did not occur. A computed tomographic scan was normal in five patients and showed MCA infarction in one (case 5). There was no preceding trauma.

Extracranial Doppler sonography showed ICA occlusion on one side in all patients and additional stenosis on the other side in case 3. Four patients had collateral blood supply from the ipsilateral ECA to ICA territory and patient 3 had collateral supply across both OpAs with retrograde flow.

Transcranial Doppler sonography showed reduced MCA-BFV and PI on the side of dissection in five patients compared with the contralateral side ($P = .001$ for BFV, $P = .002$ for PI) as well as compared with the controls ($P = .0001$ for BFV, $P = .0001$ for PI). An additional patient had symmetric MCA velocities but reduced PI on the side of the lesion (case 2). All had collateral blood supply across the anterior communicating artery from the contralateral ICA. Mean BFV and PI with the side differences of patients and controls are given in Table 2. In controls, there was a correlation between right and left MCA-BFV ($r = .955$, $F = 516.2$, $P = .0001$) and PI ($r = .768$, $F = 71.8$, $P = .0001$) and there was no side difference ($P = .83$ for both). In patients, there was no correlation between MCA-BFV ($r = .692$, $F = 3.7$, $P = .13$) and PI ($r = .242$, $F = 0.25$, $P = .64$) ipsilateral and contralateral to the dissection side, and the side differences were obvious ($P = .001$ for BFV and $P = .002$ for PI).

Duplex Examination

No patient had atherosclerotic wall changes. All the proximal ICA segments were patent on the "occluded" side, two with a residual "stump flow" and four without recordable flow signal. There was a "membrane" visible crossing the ICA lumen in four arteries, producing the picture of double lumen not compressible by the probe (Fig 1).

Table 2.—Transcranial Doppler Findings*

	L or Ipsilateral MCA		R or Contralateral MCA		Mean Difference	
Group	BFV	PI	BFV	PI	BFV	PI
Controls						
Mean ± SD	64.5 ± 10.5	0.76 ± 0.15	64.1 ± 11.6	0.75 ± 0.15	0.46 ± 3.6	0.01 ± 0.1
Range	45-90	0.48-1.24	41-90	0.51-1.37	17	0.55
Patients						
Mean ± SD	43.2 ± 9.5	0.46 ± 0.08	61.2 ± 11.4	0.65 ± 0.08	18 ± 8.4	0.2 ± 0.1
Range	33-55	0.33-0.57	48-82	0.52-0.75	24	0.26

*MCA indicates middle cerebral artery; BFV, blood flow velocity; and PI, pulsatility index. Left and right MCAs were examined in controls, ipsilateral and contralateral MCAs in patients. In cases with bilateral dissection, the ipsilateral side indicates the side more occluded.

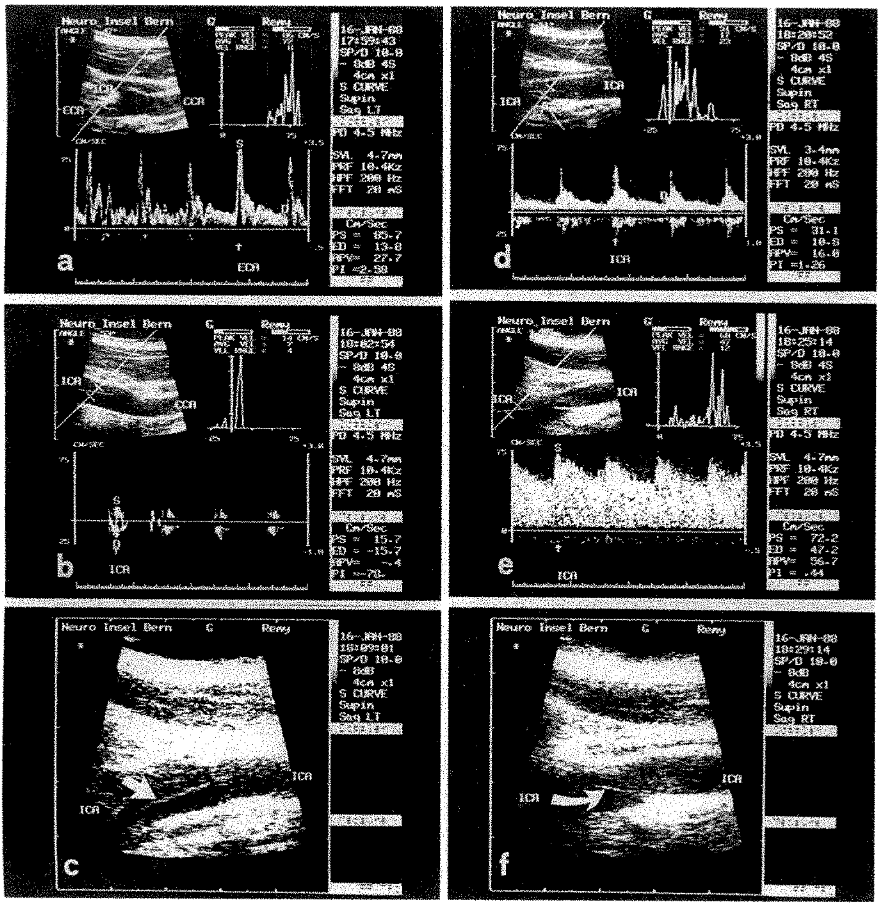

Fig 1.—Results of initial Duplex scanning (case 3): a, open left carotid bifurcation and identification of external carotid artery (ECA); b, only short systolic flow signal in the most proximal left internal carotid artery (ICA; stump flow); c, membrane (arrow) crossing lumen of left ICA in a more distal segment; d, preserved flow signal in proximal right ICA; e, high blood flow velocity indicating stenosis in more distal segment of right ICA, membrane crossing vessel lumen; and f, membrane crossing vessel lumen of right ICA (arrow). CCA indicates common carotid artery.

Angiography

Five patients (cases 1, 2, 3, 5, and 6) had bilateral, and one (case 4) had unilateral, carotid angiography. One patient (case 3) had bilateral dissection; consequently, seven dissected ICAs could be analyzed.

In all of them, the carotid bifurcation and at least the most proximal 2 cm of the ICA were normal. Four showed smoothly tapering stenoses (cases 3 [left], 4, 5, and 6) starting 3 to 4 cm distal to the bifurcation, in all extending up to the base of the skull (in case 5 probably to the siphon segment). In three, the stenoses were high grade with a filiform residual lumen resulting in a "string sign" (cases 4, 5 and 6). Abrupt return to normal caliber was noted in all at the entrance of the carotid canal. Two showed irregular segmental stenosis (cases 1 and 3 [right]), in both cases of the prepetrosal segment and with abrupt reconstitution of a normal lumen width at the entrance of the carotid canal. In case 1, stenosis started immediately distal to a carotid kinking.

There was a tapering occlusion starting 2 cm distal to the bifurcation with a flame-shaped stump in one artery (case 2). Collateral blood supply across the anterior part of the circle of Willis (anterior communicating artery) was confirmed in all five cases with bilateral carotid angiograms.

No patient showed pseudoaneurysm formation or signs indicative of fibromuscular dysplasia. None had atherosclerotic wall lesions (Fig 2). The results of ultrasound findings and angiography are summarized in Table 3.

REPORT OF A CASE

A 41-year-old technician had no vascular risk factors. Three weeks before his hospitalization, he felt increasing pain in his right temple and cheek. Plain roentgenograms showed an opacified maxillary sinus, and polyposis was considered as the likely cause of his pain. The patient was admitted for sinuscopy. Soon after premedication with intramuscular atropine sulfate (0.5 mg) and morphine chloride (5 mg), he fainted. When he regained consciousness after several minutes, there was right-sided hemiplegia and asphasia clearing within 2 hours. Physical examination revealed a bruit over the right carotid artery. Results of routine blood laboratory tests, electrocardiogram, and computed tomography were normal. Now, on detailed questioning, he reported several attacks of blurred vision or transient blindness of his right eye, lasting 1 or 2 minutes, in the days before admission. In addition, he had had three episodes of feeling cold and heaviness or loss of motor control of his right arm and hand.

Doppler analysis (Fig 3) showed reduced diastolic flow and increased PI in the left CCA. The left ICA could not be identified. The left ECA showed high diastolic flow resembling an intracranial vessel. The BFVs in the right CCA, the ECA, and the proximal part of the ICA were normal. However, in the high cervical segment of the right ICA, there was increased BFV over a long segment up to the base of the skull. Both OpAs showed reversed flow direction toward the intracranial region.

The TCD analysis (Fig 3) revealed reduced BFV and reduced PI in the left MCA. The left anterior cerebral artery showed reversal of flow direction. High BFVs in the left posterior cerebral artery indicated collateral flow from the posterior circulation.

Duplex scanning (Fig 1) showed a widely patent left proximal ICA, but only minimal systolic intraluminal flow signal (stump flow). In its more distal part, a membranelike structure traversing the vessel lumen could be visualized. The right proximal ICA was also patent, and flow was normal. Still more distally, there was a membranelike structure in the vessel lumen, and at this site high BFVs were present, indicating stenosis.

A diagnosis of left ICA occlusion and right ICA stenosis distal to their origin from the bulb was made, with collateral flow to the left carotid territory across the anterior and posterior communicating arteries. The patent proximal ICA segments and the membranes traversing the vessel lumen suggested bilateral ICDs. Cerebral four-vessel angiography (Fig 2) showed a normal proximal ICA on both sides. In the higher cervical part, the left one showed progressive narrowing to a stringlike lumen with abrupt luminal reconstitution at the entry to the petrosal canal. There was moderate stenosis of the right ICA in the higher cervical part, again with abrupt reconstitution of the vessel lumen at the base of the skull. Intracranially, flow was from the right ICA to the left across the anterior communicating artery. Because of the smooth boundaries of luminal narrowings, bilateral carotid hypoplasia was diagnosed by the radiologist (which did not explain the sudden neurologic symptoms).

Doppler control 10 days later showed normalized BFV in both CCAs. Both ICAs could be identified with normal BFV in their proximal parts but with high BFV in their upper cervical segments due to stenosis. The MCA-BFV was symmetric. The anterior cerebral artery and OpA flows were antegrade on both sides. Duplex scanning showed flow in both ICAs, but there were still stenoses due to membranelike structures. This flow reconstitution clearly made hypoplasia unlikely and a diagnosis of dissection more favorable. Doppler reexamination 2 months later showed normal results proving spontaneous recanalization and yielded the diagnosis of spontaneous bilateral ICD. The patient has remained asymptomatic taking aspirin.

COMMENT

Because the clinical presentation of ICD may be extremely variable,[2] the diagnosis cannot be made on clinical grounds alone. Carotid angiography is at present still the method of choice for definite diagnosis. Though it has become much less risky owing to technical achievements,[5-7] it remains an invasive procedure that should not be performed when there is only weak clinical suspicion of ICD. In these situations, an easily available, noninvasive method is desirable that can confirm the suspicion and allow the selective use of carotid angiography.

Conventional direct and indirect (pulsed- or continuous-wave) Doppler sonography of the extracranial carotid arteries and their branches[24] can reveal

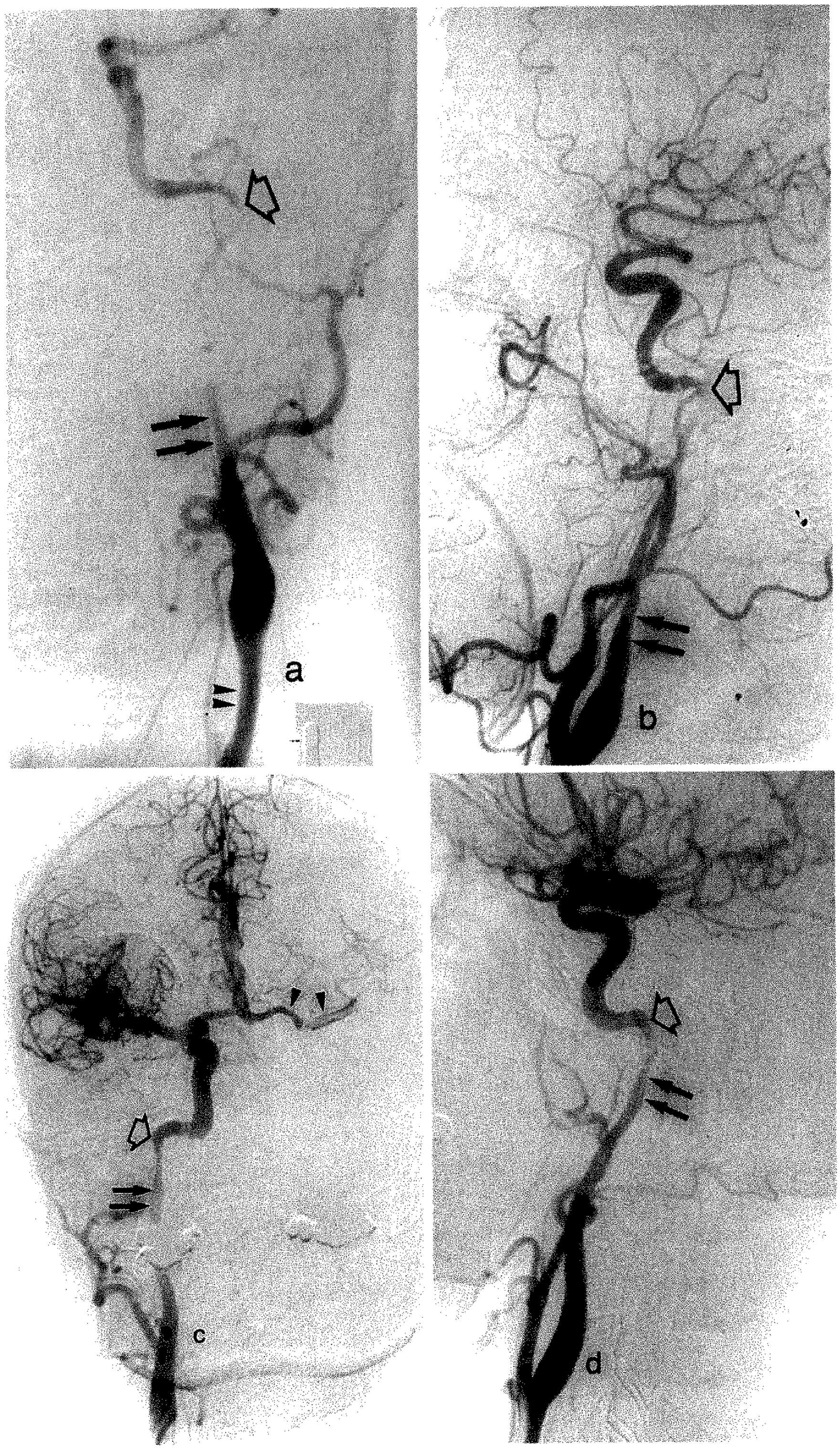

Fig 2.—Left common carotid arteriogram in case 3 (a, anteroposterior projection; b, lateral view) demonstrates common carotid narrowing (arrowheads in a) resulting from subintimal injection following direct artery puncture. Carotid bifurcation and proximal 3 cm of internal carotid artery (ICA) are normal. Then, smoothly tapering stenosis of left cervical ICA (arrows in a and b) with severe slowing of flow is noted, extending up to the skull base, where abrupt return to normal caliber is seen at entrance of carotid canal (open arrows in a and b). There is no filling of left anterior cerebral artery. Right common carotid arteriogram (c, anteroposterior projection; d, lateral view) again shows normal carotid bifurcation and proximal right ICA. Irregular segmental moderate stenosis of the high cervical prepetrosal ICA segment (arrows in c and d) is demonstrated with abrupt reconstitution of normal lumen width at the entrance of the carotid canal (open arrows in c and d). There is collateral flow from right to left carotid territory across anterior circle of Willis (arrowheads in c).

Table 3.—Summary of Results*

Patient No./ Age, y/Sex	Arteriography	ECD	TCD	Duplex Sonography
1/49/M	Segmental stenosis of high cervical R ICA; collateral flow across circle of Willis, L to R	R ICA occlusion, R OpA retrograde	R MCA BFV ↓; collateral flow across AComA, L to R	Patent proximal R ICA with stump flow
2/42/F	Tapering occlusion of L ICA; collateral flow across circle of Willis, R to L	L ICA occlusion, OpA both orthograde	L MCA PI ↓; collateral flow across AComA, R to L	Patent proximal L ICA, no intraluminal flow; membrane with double lumen
3/41/M	L ICA: string sign, reconstitution at skull base; R ICA: high cervical segmental stenosis, reconstitution at skull base; collateral flow across circle of Willis, R to L	L ICA occlusion, R ICA stenosis (high cervical segment), OpAs both retrograde (bilateral dissection)	L MCA BFV ↓; collateral flow across AComA, R to L and from vertebrobasilar system	Patent proximal L ICA without flow; membrane L ICA (distal); membrane R ICA (distal and stenosis); double lumen
4/41/M	L ICA: string sign, reconstitution at skull base	L ICA occlusion, L OpA retrograde	L MCA BFV ↓; collateral flow across AComA, R to L	Patent proximal L ICA with stump flow
5/40/M	R ICA: string sign up to cavernous segment; collateral flow across circle of Willis, L to R	R ICA occlusion, R OpA retrograde	R MCA BFV ↓; collateral flow across AComA, L to R; R MCA, no reactivity on CO_2 breathing	Patent proximal R ICA without flow
6/41/M	L ICA: string sign, reconstitution at skull base; collateral flow across circle of Willis, R to L	L ICA occlusion, L OpA retrograde	L MCA BFV ↓; collateral flow across AComA, R to L	Patent proximal L ICA without flow; membrane with double lumen not compressible

*ECD indicates extracranial Doppler sonography; TCD, transcranial Doppler sonography; ICA, internal carotid artery; OpA, ophthalmic artery; MCA, middle cerebra artery; BFV, blood flow velocity; AComA, anterior communicating artery; and PI, pulsatility index. Occlusion on ECD indicates no signal from ICA at origin from bulb an at skull base.

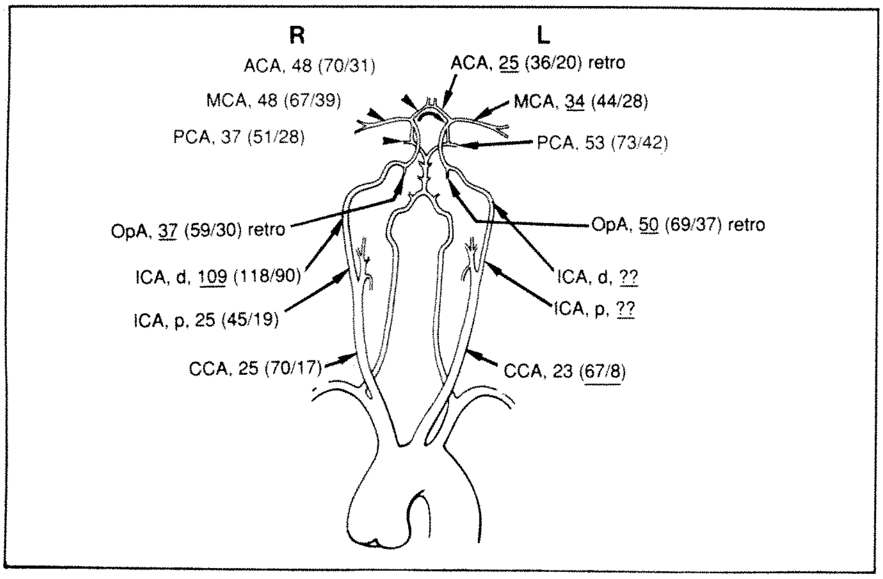

Fig 3.—Results of initial extracranial and transcranial Doppler analysis in case 3 (see text for details). ACA indicates anterior cerebral artery; retro, retrograde; MCA, middle cerebral artery; PCA, posterior cerebral artery; OpA, ophthalmic artery; ICA, internal carotid artery (d and p indicating distal and proximal); and CCA, common carotid artery. The numbers represent the values of blood flow velocities in each vessel: mean (systolic/diastolic). The pathological values are underlined.

occlusion or stenosis if it exceeds 50% of lumen diameter. The technique does not yield further information about origin. Only the finding of a stenosis located in the upper cervical ICA segment or extending over a long distance may suggest dissection,[22,29] but this is not a specific sign. Transcranial Doppler sonography,[25-28] though detecting the effects on intracranial circulation including collateral blood flow, does not help in further differentiating the origin of stenosis or occlusion.

The primary goal of CUE is the differentiation of ICD from occlusion or stenosis due to other causes such as atherosclerosis. Atherosclerotic lesions of the brain-supplying arteries show a predilection for the carotid bifurcation.[3] Spontaneous ICD, on the other hand, is usually localized in the middle or upper cervical segment of the ICA or begins at least 2 to 3 cm distal to the carotid bifurcation.[1,3,16,17,20,23] These anatomic facts and the easy accessibility of the carotid bifurcation in most patients by duplex scanning make this method suitable for differentiation.

When conventional Doppler sonography indicates ICA stenosis or occlusion, the indirect findings at duplex scanning listed in Table 4[31-34] suggest a dissection. These are ultimately nonspecific findings, and the diagnosis may be hampered when there is the simultaneous presence of atheromatous plaques[22] or when the ICD starts already at the bifurcation.[20,21] Therefore, direct visualization of the dissection should be attempted. Direct and more specific signs of ICD at duplex scanning are listed in Table 4.

Internal carotid artery dissection is virtually always extracranial but varies considerably in extent.[21] It typically occurs distal to the extracranial bifurcation,[4] often at or around the C-2 vertebral level.[2,21] Because this region may be beyond the range of carotid imaging by

Table 4.—Duplex Sonography: Findings Suggesting ICA Dissection*

- Indirect findings
  - No atheromatous plaques are visible in carotid bifurcation
  - Bulb and proximal segment of ICA are patent
  - No flow signal or high-resistance flow pattern (short, only
    systolic flow peak [stump flow] or bidirectional [reverberating] systolic flow) in proximal ICA
  - Lack of wall pulsations
- Direct signs
  - Tapering of ICA lumen starting ≥2 cm distal to bulb
  - Irregular "membrane" crossing ICA lumen (Fig 1)
  - Demonstration of true lumen with flow and false (thrombosed) lumen without flow; unlike veins, true and false lumens are noncompressible by probe pressure; flow in false lumen resulting from more distal reentry into true lumen, as frequently found in CCA dissection associated with dissecting aortic aneurysm,[31-34] is rare
  - Axial sections show "membrane" as flap in lumen
- Findings at follow-up examinations
  - Recovery of lumen patency
  - Flow recovery
  - Recovery of normal hemodynamics, when combined with TCD

*ICA indicates internal carotid artery; CCA, common carotid artery; and TCD, transcranial Doppler sonography.

Table 5.—Limitations of Duplex Sonography

- Anatomic
  - Short and / or fat neck, high cervical carotid bifurcation, goiter, calcification of atherosclerotic lesions (sound shadow)
- Individual
  - Restless, agitated, continuously swallowing patients, air emphysema; direct examination may be impossible
- Methodic
  - Occlusion cannot always be demonstrated directly because of its high cervical location
  - Usually, whole longitudinal extension of wall dissection and especially involvement of intracranial ICA segments (occurring in up to 20%[39,40]) cannot be detected
  - Detection of aneurysms is usually not possible[29]
  - Identification of fibromuscular dysplasia as underlying cause[16,39] is hardly ever possible

ultrasound, direct visualization of the ICD is not possible in all cases.[22]

Sensitivity of CUE in detecting occlusion in the case of ICD was very high in one study (95%).[22] Its emergency use in cases where clinical presentation suggests dissection does help in rapid diagnosis and selection of patients for angiography.

Duplex sonography has several methodologic limitations, listed in Table 5. These are the major reasons why I still consider angiography to be necessary to assess the full extent of the vascular process and to confirm the ultrasound findings.

In addition to its use in initial diagnosis, duplex scanning is an excellent noninvasive modality for serial follow-up examination.[29,35,36] The signs indicating recovery are listed in Table 4. Spontaneous resolution or reduction of stenosis may occur at variable intervals, ranging from a few days to several months.[19,22,29] Sequential follow-up studies have shown that this process generally occurs within a few days and only occasionally over weeks or months.[3,29,35,37-39]

Most authors agree that ischemic infarction is due in most cases to distal embolism from local thrombosis at the stenotic segment. The role of embolism is evident from the occurrence of ischemic symptoms when a stenosis is hemodynamically insignificant, from arteriography that shows distal emboli, and from intraluminal thrombus seen arteriographically and at surgery. Embolic stroke may develop in the first few days of dissection,* and its frequency is estimated to be at least 15%[3] to 24%.[21] Moreover, stenosis may progress to occlusion,[17,18,40] resulting in a critical hemodynamic situation and preventing recanalization. These potential complications are the reason why anticoagulant therapy, first with heparin, is recommended by several authors[2,42] with the idea to prevent thrombosis and embolism. It is logical that treatment should be started as early as possible, implicating early diagnosis, facilitated by application of CUE. As controlled studies are lacking, the efficacy of such therapy remains unproved, regardless of the nature and degree of the anatomic disease present. To date, no harmful effect of anticoagulant therapy, including cases with extracranial aneurysms, has been reported,[2,8,11,17,22,42] and only the simultaneous presence of an intracranial aneurysm is considered a contraindication.[2] Several uncontrolled studies suggest beneficial effects of anticoagulation.[21,22,43] On the other hand, it seems pointless to continue anticoagulant therapy once vascular patency has been restored. The CUE offers the possibility of noninvasive follow-up to detect the moment of recanalization. As spontaneous recanalization is the rule,[2-4,17,22,37,44-46] surgical interventions remain exceptional[2-4,8,37,47,48] and are reserved for patients with recurrent or progressive ischemic symptoms despite anticoagulant therapy. If these ischemic symptoms are due to insufficient collateral blood supply, it may be detected by TCD (case 5). Therefore, TCD may help in selecting patients for revascularization procedures.

In conclusion, CUE with special emphasis on duplex scanning is particularly useful to select patients with suspected ICD for arteriography and thus provides a tool for early diagnosis by its emergency use. It is the method of choice for follow-up examinations to determine duration of anticoagulation and may help to assess the real frequency of ICD when also used in patients in whom angiography would not be considered.

I wish to thank Peter Huber, director of the Department of Neuroradiology, University of Bern, Switzerland, for performing the neuroradiologic examinations.

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*References 3, 4, 17, 18, 20, 23, 37, 40, and 41.

References

1. Hart RG, Easton JD. Dissection of cervical and cerebral arteries. *Neurol Clin.* 1983;1:155-182.

2. Houser WO, Mokri B, Sundt TM, Baker HL, Reese DF. Spontaneous cervical cephalic arterial dissection and its residuum: angiographic spectrum. *AJNR.* 1984;5:27-34.

3. Gauthier G, Rohr J, Wildi E, Megret M. L'hématome disséquant spontané de l'artère carotide interne. *Arch Suisses Neurol Psychiatr.* 1985; 136:53-74.

4. Hart RG, Easton JD. Dissection and trauma of cervico-cerebral arteries. In: Barnett HJM, ed. *Stroke, Pathophysiology, Diagnosis and Management.* New York, NY: Churchill Livingstone Inc; 1986:775-788.

5. Smoker WRK, Biller J, Hingtgen WL, Adams HP, Toffol GJ. Angiography of nonhemorrhagic cerebral infarction in young adults. *Stroke.* 1987;18:708-711.

6. Earnest F, Forbes G, Sandok PA, et al. Complications of cerebral angiography: prospective assessment of risk. *AJR Am J Roentgenol.* 1985; 142:247-253.

7. Patterson RH, Goodell H, Dunning HS. Complications of carotid angiography. *Arch Neurol.* 1964;10:513-520.

8. Mokri B, Sundt TM, Houser OW, Piepgras DG. Spontaneous dissection of the cervical internal carotid artery. *Ann Neurol.* 1986;19:126-138.

9. Hart RG, Miller VT. Cerebral infarction in young adults: a practical approach. *Stroke.* 1983; 14:110-114.

10. Bogousslavsky J, Regli F. Ischemic stroke in adults younger than 30 years of age. *Arch Neurol.* 1987;44:479-482.

11. Bogousslavsky J, Despland PA, Regli F. Spontaneous carotid dissection with acute stroke. *Arch Neurol.* 1987;44:137-140.

12. Biller J, Hingtgen WL, Adams HP, Smoker WRK, Godersky JC, Toffol GJ. Cervicocephalic arterial dissections: a ten-year experience. *Arch Neurol.* 1986;43:1234-1238.

13. Francis KR, Williams DP, Troost BT. Facial numbness and dysesthesia, new features of carotid artery dissection. *Arch Neurol.* 1987;44:345-346.

14. Goldberg HI, Grossmann RI, Gomory JM, Ashbury AK, Bilaniuk LT, Zimmermann RA. Cervical internal carotid artery dissecting hemorrhage: diagnosis using MRI. *Radiology.* 1986; 158:157-161.

15. Maitland CH, Black J, Smith W. Abducens

nerve palsy due to spontaneous dissection of the internal carotid artery. *Arch Neurol.* 1983;40:448-449.

16. Bradac GB, Kaernbach A, Bolk-Weischedel D, Finck GA. Spontaneous dissecting aneurysm of cervical cerebral arteries. *Neuroradiology.* 1981; 21:149-154.

17. Fisher CM, Ojemann RG, Roberson GH. Spontaneous dissection of cervico-cerebral arteries. *Can J Neurol Sci.* 1978;5:9-19.

18. Ehrenfeld WK, Wylie EJ. Spontaneous dissection of the internal carotid artery. *Arch Surg.* 1976;111:1294-1301.

19. Quisling RG, Friedman WA, Rhoton AL. High cervical carotid artery dissection: spontaneous resolution. *AJNR.* 1980;1:463-468.

20. O'Dwyer JA, Moscow N, Trevor R, Ehrenfeld WK, Newton TH. Spontaneous dissection of the carotid artery. *Radiology.* 1980;137:379-385.

21. Sellier N, Chiras J, Benhamou M, Bories J. Dissections spontanées de la carotide interne: aspects cliniques, radiologiques et évolutifs: a propos de 46 cas. *J Neuroradiol.* 1983;10:243-259.

22. De Bray JM, Dubas F, Joseph PA, Causeret H, Pasquier JP, Emile E. Etude ultrasonique de 22 dissections carotidiennes. *Rev Neurol.* 1989;145:702-709.

23. Petro GR, Witwer GA, Cacayorin ED, et al. Spontaneous dissection of the cervical internal carotid artery: correlation of arteriography, CT and Pathology. *AJNR.* 1986;7:1053-1058.

24. von Reutern GM, Büdingen HJ. *Ultraschalldiagnostik der hirnversorgenden Arterien.* Stuttgart, Germany: Georg Thieme Verlag; 1989.

25. Aaslid R. *Transcranial Doppler Sonography.* New York, NY: Springer-Verlag NY Inc; 1986.

26. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. *J Neurosurg.* 1982;57:769-774.

27. Lindegaard KF, Bakke SJ, Grolimund P, Aaslid R, Huber P, Nornes H. Assessment of intracranial hemodynamics in carotid artery disease by transcranial Doppler ultrasound. *J Neurosurg.* 1985;63:890-898.

28. Arnolds BJ, von Reutern GM. Transcranial Doppler sonography: examination technique and normal reference values. *Ultrasound Med Biol.* 1986;12:115-123.

29. Hennerici M, Steinke W, Rautenberg W. High-resistance Doppler flow pattern in extracranial carotid dissection. *Arch Neurol.* 1989;46:670-672.

30. Hass WK, Fields WS, North RR, Kricheff II, Chase NE, Bauer RB. Joint study of extracranial occlusion, II: arteriography, techniques, sites and complications. *JAMA.* 1968;203:962-968.

31. Zirkle PK, Wheeler JR, Gregory RT, Snyder SO, Gayle RG, Sorrell K. Carotid involvement in aortic dissection diagnosed by duplex scanning. *J Vasc Surg.* 1984;1:700-703.

32. Hirst AE, Johns VJ, Kime SW. Dissecting aneurysms of the aorta: a review of 505 cases. *Medicine.* 1958;37:217-279.

33. Bashour TT, Crew JP, Dean M, Hanna ES. Ultrasonic imaging of common carotid artery dissection. *J Clin Ultrasound.* 1985;13:210-211.

34. Zurbrügg HR, Leupi F, Schüpbach P, Althaus U. Duplex scanner study of carotid artery dissection following surgical treatment of aortic dissection type A. *Stroke.* 1988;19:970-976.

35. Rothrock JF, Lym V, Press G, Gosink B. Serial magnetic resonance and carotid duplex examinations in the management of carotid dissection. *Neurology.* 1989;39:686-692.

36. Benrabah R, Bousser RG, Cabanis EA, Lopez A, Moreau J. Syndrome de Claude-Bernard-Horner douloureux revelateur d'une dissection spontanée de l'artère carotide interne: interet du bilan ultrasonique cervical: a propos de deux observations. *Bull Soc Ophtalmol Fr.* 1988;88:763-768.

37. Pozzati E, Gaist G, Poppi M. Resolution of occlusion in spontaneously dissected carotid arteries. *J Neurosurg.* 1982;56:857-860.

38. Cusick JF, Daniels D. Spontaneous reversal of internal carotid artery occlusion. *J Neurosurg.* 1981;54:811-813.

39. Gee W, Kaupp HA, McDonald KM. Spontaneous dissection of internal carotid arteries: spontaneous resolution documented by serial ocular-pneumoplethysmography and angiography. *Arch Surg.* 1980;115:944-949.

40. Friedman WA, Day AL, Quisling RG, Sypert GW, Rhoton AL. Cervical carotid dissecting aneurysms. *Neurosurgery.* 1980;7:207-214.

41. Stringer WL, Kelly DL. Traumatic dissection of the extracranial internal carotid artery. *Neurosurgery.* 1980;6:123-130.

42. McNeill DH, Dreisbach J, Marsden RJ. Spontaneous dissection of the internal carotid artery: its conservative management with heparin sodium. *Arch Neurol.* 1980;37:54-55.

43. Marx A, Messing B, Storch B, Busse O. Spontane Dissektion hirnversorgender Arterien. *Nervenarzt.* 1987;58:8-18.

44. Cusmano F, Piazza P, De Donatis M, Montanari E, Saginario A, Bassi P. Dissecazione dell' arteria carotide interna. *Radiol Med.* 1988;76:262-273.

45. Parenti G, Marconi F, Canapicchi R, Puglioli M, Giradli C. Spontaneous recanalization of carotid artery occlusion following non traumatic dissection. *Ital J Neurol Sci.* 1989;10:361-367.

46. Markwalder TM, Starrett RW, Mumenthaler M. Spontaneous bilateral recanalization in bilateral internal carotid artery occlusion. *Stroke.* 1980;11:95-97.

47. Landre E, Roux FX, Cioloca C. Dissection spontanée de la carotide interne exocranienne: aspects thérapeutiques. *Presse Med.* 1987;16:1273-1276.

48. Hart RG, Easton JD. Dissections. *Stroke.* 1985;16:925-927.

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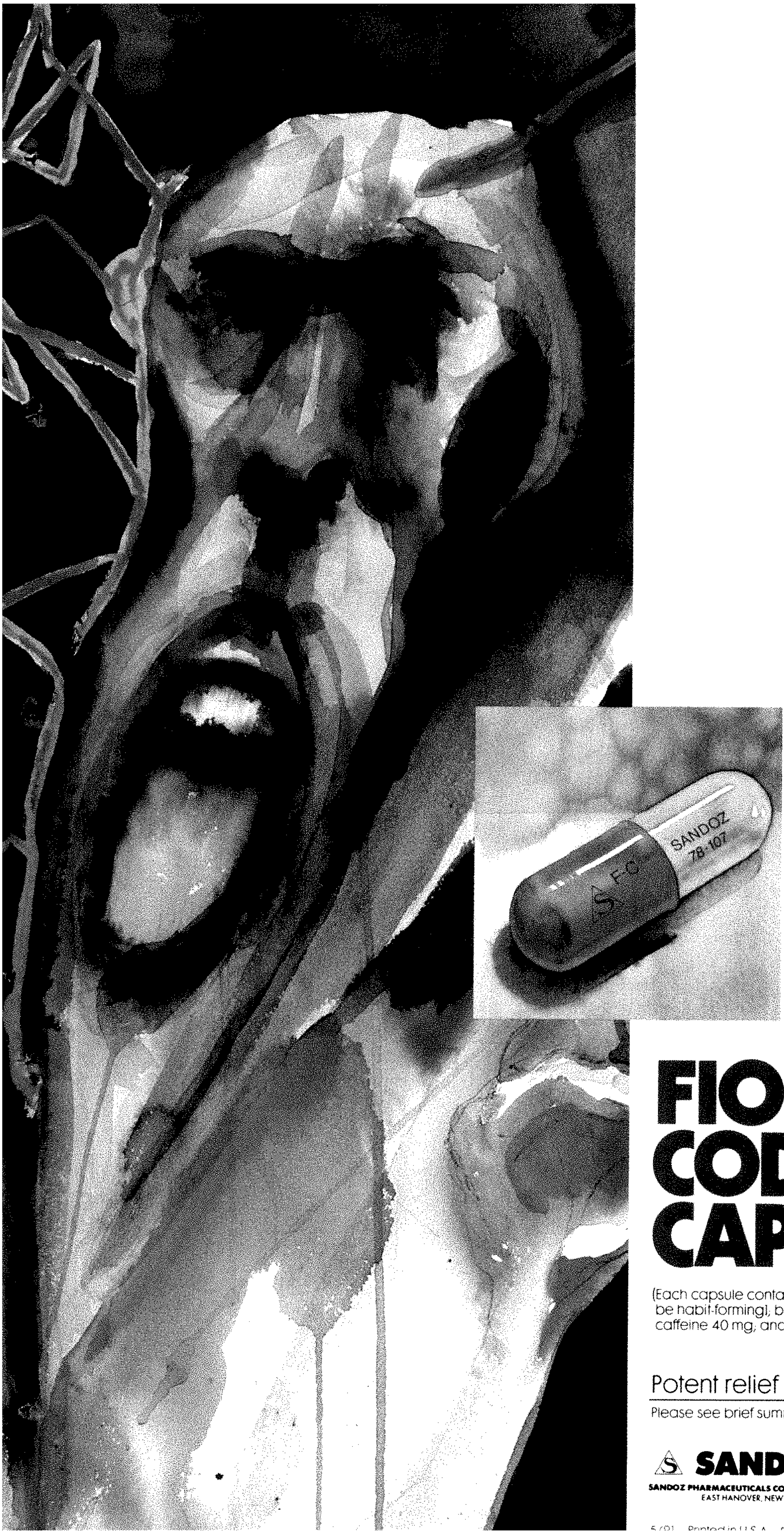

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"Headache"– a personal interpretation of headache pain by John Crowley, a headache patient.

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(Each capsule contains: codeine phosphate 30 mg [Warning: May be habit-forming]; butalbital 50 mg [Warning: May be habit-forming]; caffeine 40 mg; and aspirin 325 mg)

Potent relief of tension headache pain

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BRIEF SUMMARY: Please see package insert for full prescribing information.

FIORINAL® WITH CODEINE CIII CAPSULES

(Codeine phosphate USP, 30 mg [warning: may be habit forming], butalbital USP, 50 mg [warning: may be habit forming]; caffeine USP, 40 mg; aspirin USP, 325 mg)

CAUTION: Federal law prohibits dispensing without prescription.

CONTRAINDICATIONS: Fiorinal® with Codeine is contraindicated under the following conditions:

1. Hypersensitivity or intolerance to aspirin, caffeine, butalbital or codeine.
2. Patients with a hemorrhagic diathesis (e.g., hemophilia, hypoprothrombinemia, von Willebrand's disease, the thrombocytopenias, thrombasthenia and other ill-defined hereditary platelet dysfunctions, severe vitamin K deficiency and severe liver damage.)
3. Patients with the syndrome of nasal polyps, angioedema and bronchospastic reactivity to aspirin or other nonsteroidal anti-inflammatory drugs. Anaphylactoid reactions have occurred in such patients.
4. Peptic ulcer or other serious gastrointestinal lesions.
5. Patients with porphyria.

WARNINGS: Therapeutic doses of aspirin can cause anaphylactic shock and other severe allergic reactions. It should be ascertained if the patient is allergic to aspirin, although a specific history of allergy may be lacking.

Significant bleeding can result from aspirin therapy in patients with peptic ulcer or other gastrointestinal lesions, and in patients with bleeding disorders.

Aspirin administered pre-operatively may prolong the bleeding time.

In the presence of head injury or other intracranial lesions, the respiratory depressant effects of codeine and other narcotics may be markedly enhanced, as well as their capacity for elevating cerebrospinal fluid pressure. Narcotics also produce other CNS depressant effects, such as drowsiness, that may further obscure the clinical course of patients with head injuries.

Codeine or other narcotics may obscure signs on which to judge the diagnosis or clinical course of patients with acute abdominal conditions.

Butalbital and codeine are both habit-forming and potentially abusable. Consequently, the extended use of Fiorinal® with Codeine is not recommended.

Results from epidemiologic studies indicate an association between aspirin and Reye Syndrome. Caution should be used in administering this product to children, including teenagers, with chicken pox or flu.

PRECAUTIONS: General: Fiorinal® with Codeine should be prescribed with caution for certain special-risk patients such as the elderly or debilitated, and those with severe impairment of renal or hepatic function, coagulation disorders, or head injuries.

Aspirin should be used with caution in patients on anticoagulant therapy and in patients with underlying hemostatic defects.

Precautions should be taken when administering salicylates to persons with known allergies. Hypersensitivity to aspirin is particularly likely in patients with nasal polyps, and relatively common in those with asthma.

Information for Patients: Patients should be informed that Fiorinal® with Codeine contains aspirin and should not be taken by patients with an aspirin allergy.

Fiorinal® with Codeine may impair the mental and/or physical abilities required for performance of potentially hazardous tasks such as driving a car or operating machinery. Such tasks should be avoided while taking Fiorinal® with Codeine.

Alcohol and other CNS depressants may produce an additive CNS depression when taken with Fiorinal® with Codeine, and should be avoided.

Codeine and butalbital may be habit-forming. Patients should take the drug only for as long as it is prescribed, in the amounts prescribed, and no more frequently than prescribed.

Laboratory Tests: In patients with severe hepatic or renal disease, effects of therapy should be monitored with serial liver and/or renal function tests.

Drug Interactions: The CNS effects of butalbital may be enhanced by monoamine oxidase (MAO) inhibitors.

In patients receiving concomitant corticosteroids and chronic use of aspirin, withdrawal of corticosteroids may result in salicylism because corticosteroids enhance renal clearance of salicylates and their withdrawal is followed by return to normal rates of renal clearance.

Fiorinal® with Codeine may enhance the effects of:

1. Oral anticoagulants, causing bleeding by inhibiting prothrombin formation in the liver and displacing anticoagulants from plasma protein binding sites.
2. Oral antidiabetic agents and insulin, causing hypoglycemia by contributing an additive effect, if dosage of Fiorinal® with Codeine exceeds maximum recommended daily dosage.
3. 6-mercaptopurine and methotrexate, causing bone marrow toxicity and blood dyscrasias by displacing these drugs from secondary binding sites, and, in the case of methotrexate, also reducing its excretion.
4. Non-steroidal anti-inflammatory agents, increasing the risk of peptic ulceration and bleeding by contributing additive effects.
5. Other narcotic analgesics, alcohol, general anesthetics, tranquilizers such as chlordiazepoxide, sedative-hypnotics, or other CNS depressants, causing increased CNS depression.

Fiorinal® with Codeine may diminish the effects of: Uricosuric agents such as probenecid and sulfinpyrazone, reducing their effectiveness in the treatment of gout. Aspirin competes with these agents for protein binding sites.

Drug/Laboratory Test Interactions

Aspirin: Aspirin may interfere with the following laboratory determinations in blood: serum amylase, fasting blood glucose, cholesterol, protein, serum glutamic-oxalacetic transaminase (SGOT), uric acid, prothrombin time and bleeding time. Aspirin may interfere with the following laboratory determinations in urine: glucose, 5-hydroxyindoleacetic acid, Gerhardt ketone, vanillylmandelic acid (VMA), uric acid, diacetic acid, and spectrophotometric detection of barbiturates.

Codeine: Codeine may increase serum amylase levels.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Adequate long-term studies have been conducted in mice and rats with aspirin, alone or in combination with other drugs, in which no evidence of carcinogenesis was seen. No adequate studies have been conducted in animals to determine whether aspirin has a potential for mutagenesis or impairment of fertility. No adequate studies have been conducted in animals to determine whether butalbital has a potential for carcinogenesis, mutagenesis, or impairment of fertility.

Usage in Pregnancy

Teratogenic Effects: Pregnancy Category C — Animal reproduction studies have not been conducted with Fiorinal® with Codeine. It is also not known whether Fiorinal® with Codeine can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Fiorinal® with Codeine should be given to a pregnant woman only when clearly needed.

Nonteratogenic Effects: Although Fiorinal® with Codeine was not implicated in the birth defect, a female infant was born with lissencephaly, pachygyria and heterotopic gray matter. The infant was born 8 weeks prematurely to a woman who had taken an average of 90 Fiorinal® with Codeine capsules each month from the first few days of pregnancy. The child's development was mildly delayed and from one year of age she had partial simple motor seizures.

Withdrawal seizures were reported in a two-day-old male infant whose mother had taken a butalbital-containing drug during the last 2 months of pregnancy. Butalbital was found in the infant's serum. The infant was given phenobarbital 5mg/kg, which was tapered without further seizure or other withdrawal symptoms.

Studies of aspirin use in pregnant women have not shown that aspirin increases the risk of abnormalities when administered during the first trimester of pregnancy. In controlled studies involving 41,337 pregnant women and their offspring, there was no evidence that aspirin taken during pregnancy caused stillbirth, neonatal death or reduced birth weight. In controlled studies of 50,282 pregnant women and their offspring, aspirin administration in moderate and heavy doses during the first four lunar months of pregnancy showed no teratogenic effect.

Reproduction studies have been performed in rabbits and rats at doses up to 150 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to codeine.

Therapeutic doses of aspirin in pregnant women close to term may cause bleeding in mother, fetus, or neonate. During the last 6 months of pregnancy, regular use of aspirin in high doses may prolong pregnancy and delivery.

Labor and Delivery: Ingestion of aspirin prior to delivery may prolong delivery or lead to bleeding in the mother or neonate. Use of codeine during labor may lead to respiratory depression in the neonate.

Nursing Mothers: Aspirin, caffeine, barbiturates and codeine are excreted in breast milk in small amounts, but the significance of their effects on nursing infants is not known. Because of potential for serious adverse reactions in nursing infants from Fiorinal® with Codeine, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in children below the age of 12 have not been established.

ADVERSE REACTIONS: Commonly Observed: The most commonly reported adverse events associated with the use of Fiorinal® with Codeine and not reported at an equivalent incidence by placebo-treated patients were nausea and/or abdominal pain, drowsiness, and dizziness.

Associated with Treatment Discontinuation: Of the 382 patients treated with Fiorinal® with Codeine in controlled clinical trials, three (0.8%) discontinued treatment with Fiorinal® with Codeine because of adverse events. One patient each discontinued treatment for the following reasons: gastrointestinal upset; lightheadedness and heavy eyelids; and drowsiness and generalized tingling.

Incidence in Controlled Clinical Trials: The following table summarizes the incidence rates of the adverse events reported by at least 1% of the Fiorinal® with Codeine treated patients in controlled clinical trials comparing Fiorinal® with Codeine to placebo, and provides a comparison to the incidence rates reported by the placebo-treated patients.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators.

Adverse Events Reported by at Least 1% of Fiorinal® with Codeine Treated Patients During Placebo Controlled Clinical Trials

	Incidence Rate of Adverse Events	
Body System/ Adverse Event	Fiorinal®/Codeine (N = 382)	Placebo (N = 377)
Central Nervous		
Drowsiness	2.4%	0.5%
Dizziness/Lightheadedness	2.6%	0.5%
Intoxicated Feeling	1.0%	0%
Gastrointestinal		
Nausea/Abdominal Pain	3.7%	0.8%

Other Adverse Events Reported During Controlled Clinical Trials: The listing that follows represents the proportion of the 382 patients exposed to Fiorinal® with Codeine while participating in the controlled clinical trials who reported, on at least one occasion, an adverse event of the type cited. All reported adverse events, except those already presented in the previous table, are included. It is important to emphasize that, although the adverse events reported did occur while the patient was receiving Fiorinal® with Codeine, the adverse events were not necessarily caused by Fiorinal® with Codeine.

Adverse events are classified by body system and frequency. "Frequent" is defined as an adverse event which occurred in at least 1/100 (1%) of the patients; all adverse events listed in the previous table are frequent. "Infrequent" is defined as an adverse event that occurred in less than 1/100 patients but at least 1/1000 patients. All adverse events tabulated below are classified as infrequent.

Central Nervous: headache, shaky feeling, tingling, agitation, fainting, fatigue, heavy eyelids, high energy, hot spells, numbness, and sluggishness.

Autonomic Nervous: dry mouth and hyperhidrosis.

Gastrointestinal: vomiting, difficulty swallowing, and heartburn.

Cardiovascular: tachycardia.

Musculoskeletal: leg pain and muscle fatigue.

Genitourinary: diuresis.

Miscellaneous: pruritus, fever, earache, nasal congestion, and tinnitus.

Voluntary reports of adverse drug events, temporally associated with Fiorinal® with Codeine, that have been received since market introduction and that were not reported in clinical trials by the patients treated with Fiorinal® with Codeine, are listed below. Many or most of these events may have no causal relationship with the drug and are listed according to body system.

Central Nervous: Abuse, addiction, anxiety, depression, disorientation, hallucination, hyperactivity, insomnia, libido decrease, nervousness, neuropathy, psychosis, sedation, sexual activity increase, slurred speech, twitching, unconsciousness, vertigo.

Autonomic Nervous: epistaxis, flushing, miosis, salivation.

Gastrointestinal: anorexia, appetite increased, constipation, diarrhea, esophagitis, gastroenteritis, gastrointestinal spasm, hiccup, mouth burning, pyloric ulcer.

Cardiovascular: chest pain, hypotensive reaction, palpitations, syncope.

Skin: erythema, erythema multiforme, exfoliative dermatitis, hives, rash, toxic epidermal necrolysis.

Urinary: kidney impairment, urinary difficulty.

Miscellaneous: allergic reaction, anaphylactic shock, cholangiocarcinoma, drug interaction with erythromycin (stomach upset), edema.

The following adverse drug events may be borne in mind as potential effects of the components of Fiorinal® with Codeine. Potential effects of high dosage are listed in the *OVERDOSAGE* section of this insert.

Asprin: occult blood loss, hemolytic anemia, iron deficiency anemia, gastric distress, heartburn, nausea, peptic ulcer, prolonged bleeding time, acute airway obstruction, renal toxicity when taken in high doses for prolonged periods, impaired urate excretion, hepatitis.

Caffeine: cardiac stimulation, irritability, tremor, dependence, nephrotoxicity, hyperglycemia.

Codeine: nausea, vomiting, drowsiness, lightheadedness, constipation, pruritus.

DRUG ABUSE AND DEPENDENCE: Fiorinal® with Codeine is controlled by the Drug Enforcement Administration and is classified under Schedule III.

Codeine: Codeine can produce drug dependence of the morphine type and, therefore, has the potential for being abused. Psychological dependence, physical dependence, and tolerance may develop upon repeated administration and it should be prescribed and administered with the same degree of caution appropriate to the use of other oral narcotic medications.

Butalbital: *Barbiturates may be habit forming:* Tolerance, psychological dependence, and physical dependence may occur especially following prolonged use of high doses of barbiturates. The average daily dose for the barbiturate addict is usually about 1,500 mg. As tolerance to barbiturates develops, the amount needed to maintain the same level of intoxication increases; tolerance to a fatal dosage, however, does not increase more than two-fold. As this occurs, the margin between an intoxication dosage and fatal dosage becomes smaller. The lethal dose of a barbiturate is far less if alcohol is also ingested. Major withdrawal symptoms (convulsions and delirium) may occur within 16 hours and last up to 5 days after abrupt cessation of these drugs. Intensity of withdrawal symptoms gradually declines over a period of approximately 15 days. Treatment of barbiturate dependence consists of cautious and gradual withdrawal of the drug. Barbiturate-dependent patients can be withdrawn by using a number of different withdrawal regimens. One method involves initiating treatment at the patient's regular dosage level and gradually decreasing the daily dosage as tolerated by the patient.

OVERDOSAGE: The toxic effects of acute overdosage of Fiorinal® with Codeine capsules are attributable mainly to the barbiturate and codeine components, and, to a lesser extent, aspirin. Because toxic effects of caffeine occur in very high dosages only, the possibility of significant caffeine toxicity from Fiorinal® with Codeine overdosage is unlikely.

Signs and Symptoms: Symptoms attributable to *acute barbiturate poisoning* include drowsiness, confusion, and coma; respiratory depression; hypotension; shock. Symptoms attributable to *acute aspirin poisoning* include hyperpnea, acid-base disturbances with development of metabolic acidosis, vomiting and abdominal pain; tinnitus, hyperthermia; hypoprothrombinemia; restlessness; delirium; convulsions. *Acute caffeine poisoning* may cause insomnia, restlessness, tremor, and delirium; tachycardia and extrasystoles. Symptoms of *acute codeine poisoning* include the triad of: pinpoint pupils, marked depression of respiration, and loss of consciousness. Convulsions may occur.

Treatment: The following paragraphs describe one approach to the treatment of overdose with Fiorinal® with Codeine. However, because strategies for the management of an overdose continually evolve, consultation with a regional poison control center is strongly encouraged.

Treatment consists primarily of management of barbiturate intoxication, reversal of the effects of codeine, and the correction of the acid-base imbalance due to salicylism. Vomiting should be induced mechanically or with emetics in the conscious patient. Gastric lavage may be used if the pharyngeal and laryngeal reflexes are present and if less than 4 hours have elapsed since ingestion. A cuffed endotracheal tube should be inserted before gastric lavage of the unconscious patient and when necessary to provide assisted respiration. Diuresis, alkalinization of the urine, and correction of electrolyte disturbances should be accomplished through administration of intravenous fluids such as 1% sodium bicarbonate and 5% dextrose in water.

Meticulous attention should be given to maintaining adequate pulmonary ventilation. Correction of hypotension may require the administration of levarterenol bitartrate or phenylephrine hydrochloride by intravenous infusion. In severe cases of intoxication, peritoneal dialysis, hemodialysis, or exchange transfusion may be lifesaving. Hypoprothrombinemia should be treated with vitamin K, intravenously.

Methemoglobinemia over 30% should be treated with methylene blue by slow intravenous administration.

Naloxone, a narcotic antagonist, can reverse respiratory depression and coma associated with opioid overdose. Typically, a dose of 0.4 mg to 2 mg is given parenterally and may be repeated if an adequate response is not achieved. Since the duration of action of codeine may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. A narcotic antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Toxic and Lethal Doses:

Butalbital: toxic dose 1.0 g (adult); lethal dose 2.0-5.0 g
Aspirin: toxic blood level greater than 30 mg/100 mL; lethal dose 10-30 g (adult)
Caffeine: toxic dose greater than 1.0 g; lethal dose unknown
Codeine: lethal dose 0.5-1.0 g (adult)

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[NOVEMBER 1, 1990 FWC-Z26]

High-Intensity Area in the Deep White Matter Indicating Hemodynamic Compromise in Internal Carotid Artery Occlusive Disorders

Hiroshi Yamauchi, MD; Hidenao Fukuyama, MD; Shinya Yamaguchi, MD;
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• We used positron emission tomography and magnetic resonance imaging to evaluate 16 patients with transient ischemic attacks or minor strokes and unilateral internal carotid occlusive disease, five with stenosis, and 11 with occlusion. Cerebral blood flow, cerebral metabolic rate of oxygen, oxygen extraction fraction, cerebral blood volume, and T_2-weighted magnetic resonance images obtained at 1.5-T were analyzed. Irrespective of vascular disease, patients with a confluent high-intensity area in the middle centrum semiovale had substantially decreased cerebral blood flow and ratio of cerebral blood flow to blood volume in the middle cerebral artery distribution of the cortex, with a substantially increased oxygen extraction fraction. We concluded that the confluent high-intensity area in the deep white matter region indicates hemodynamic compromise in the affected hemisphere in internal carotid artery occlusive disease.

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Magnetic resonance imaging (MRI), especially T_2-weighted images, has been found to be very sensitive in the detection of cerebral white matter disease.[1] However, whether high signal intensity in the periventricular or paraventricular regions on T_2-weighted images may indicate a pathologic state or may be of no importance remains uncertain.[2]

Hypoperfusion secondary to internal carotid artery (ICA) occlusion often results in cerebral infarction involving the deep white matter, especially the watershed zone between the distribution of the anterior cerebral artery and middle cerebral artery (MCA), with sparing of the cortical surface.[3-6] This may be because the subcortical watershed zone supplied by the most distal branches of the cortical perforating arteries is most susceptible to a reduction in perfusion pressure,[7] although the regional differences in the capacity for collateral vessel blood supply must be considered.[8] This speculation supports the hypothesis that ischemic change in the middle centrum semiovale, the most distal white matter region supplied by the

Fig 1.—Examples of high-intensity lesions on T_2-weighted magnetic resonance images (repetition time, 2000 msec; echo time, 80 msec). Left, Confluent high-intensity area in the middle centrum semiovale (arrow) in patient 13. Middle, Immediate subcortical patchy high-intensity area in patient 8. Right, Immediate subcortical punctate high-intensity areas in patient 2. Upper and lower rows correspond to the levels of the centrum semiovale and the body of the lateral ventricle, respectively.

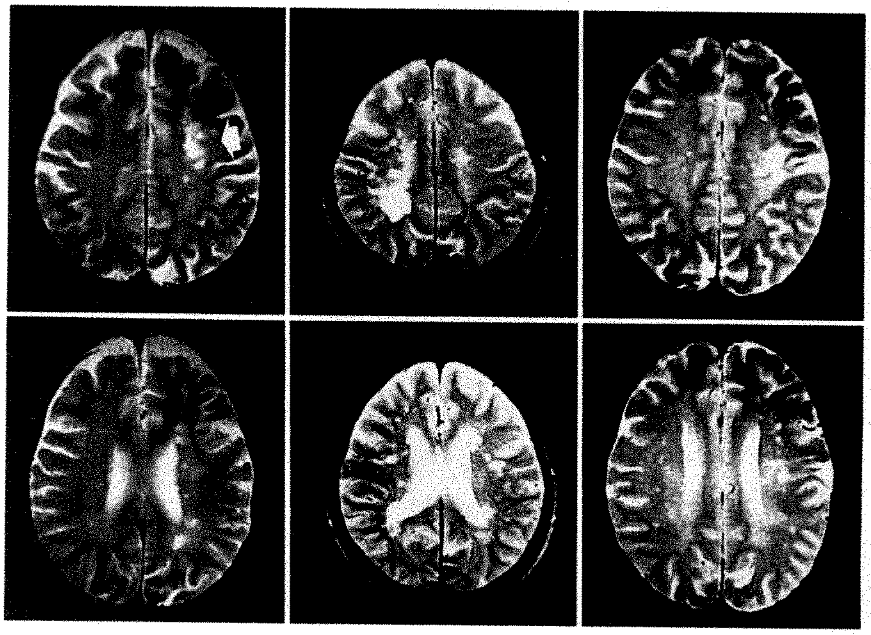

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Table 1.—Clinical and Radiographic Data on 16 Patients With Carotid Artery Occlusive Disease*

Patient/ Age, y/ Sex	Associated Condition	Presentation	Physical Examination	Angiography (4 Axis)	Infarct at CT
Group ICS(−)					
1/65/M	HT	TIA (once), amaurosis fugax (L, once)	Normal	L ICA 90% stenosis	None
2/72/F	HT	TIA (once), minor stroke	Mild L-sided hemiparesis	R ICA 95% stenosis	R parietal subcortex
3/63/F	DM	TIA (once), minor stroke,	L-sided upper limb drift	R ICA siphon 80% stenosis	R parietal subcortex
4/53/M	None	Minor stroke	Mild L-sided hemiparesis	R ICA 70% stenosis	R parietal subcortex
5/63/M	HT	TIA (once), Minor stroke	Mild R-sided hemiparesis	L ICA siphon 90% stenosis	L corona radiata
Group ICO(−)					
6/67/M	Gout	TIA (once)	Normal	L ICA occ.	None
7/63/M	None	TIA (once)	Normal	R ICA occ.	None
8/58/F	None	TIA (once), minor stroke	Mild R-sided sensory disturbance	L ICA occ.	L parietal subcortex
9/60/M	HT	TIA (once)	Normal	R ICA occ.	None
10/70/M	None	TIA (once)	Normal	R ICA occ.	None
11/56/M	Angina pectoris	Minor stroke	Mild L-sided hemiparesis	R ICA occ.	R frontal subcortex
Group ICO(+)					
12/57/M	None	TIA (once)	Normal	R ICA occ.	None
13/58/M	HT	Amaurosis fugax (R, twice), TIAs (frequent)	R-sided upper limb drift	L ICA occ., R ICA 30% stenosis	None
14/57/M	None	TIA (twice)	R-sided upper limb drift	L ICA occ., R ICA 30% stenosis	None
15/46/M	DM	Minor stroke	Mild L-sided upper limb weakness	R ICA occ., L ICA siphon 40% stenosis	R centrum semiovale
16/58/M	None	Minor stroke	Mild L-sided hemiparesis	R ICA occ.	R centrum semiovale

*CT indicates computed tomography; HT, hypertension; DM, diabetes mellitus; occ., occlusion; TIA, transient ischemic attack; ICA, internal carotid artery; MCA, middle cerebral artery; VB, vertebrobasilar artery; VA, vertebral artery; ICS(−), patients with stenosis without the high-intensity area in the middle centrum semiovale; ICO(−), patients with occlusion without high-intensity area; and ICO(+), patients with occlusion with high-intensity area.

ICA, indicates hemodynamic compromise in the affected hemisphere in carotid occlusive diseases.

Our purpose was to evaluate the relationship between the cortical hemodynamic status and the presence of a white matter high-intensity area on MRI in carotid occlusive disease and to examine the high-intensity area as a sign of hemodynamic compromise.

PATIENTS AND METHODS

Patients

Our study involved 16 patients with unilateral ICA occlusive disease, five with stenosis (>70% diameter reduction) and 11 with occlusion. Neurologic histories of the 16 patients consisted of eight with transient ischemic attacks and eight with minor completed strokes, all related to the affected carotid distribution. Our criteria for selection were as follows; (1) In all patients with ICA stenosis (ICS), the carotid artery distribution of the affected hemisphere was perfused through the stenosed carotid artery proper on angiography. All patients with ICA occlusion (ICO) had collateral vessel circulation through the anterior portion of the circle of Willis. In these two categories of carotid artery disease, the centrum semiovale is the most distal white matter area perfused by the stenosed carotid artery or the collateral vessel circulation through the anterior communicating artery. (2) All patients had, at most, only minor subcortical abnormalities (<1.5 cm in diameter) in the region supplied by the MCA on the side involved by carotid artery disease on computed tomography (CT).

Positron Emission Tomographic (PET) Measurement

Specifications of our PET scanner have been reported elsewhere.[9] In brief, it consists of four rings of 192 bismuth germanate detectors, providing seven slices with each scan. The device offers the best spatial resolution of 7.6 mm in full width half maximum at the center of the scan field and axial resolution of 12 mm at the center. Blood was sampled through cannulation of the brachial artery three times during a scanning process to determine oxygen 15 activity and arterial blood gases. Before the study, transmission scanning with germanium 68-gallium 68 was performed for 20 minutes for attenuation correction. We determined calibration factors between the PET scanner and the well counter in every study, as well as the calibration factor of cross-planes of the PET scanner. A dead time correction and a scatter correction were performed on obtained data. Image data were processed with an image processing computer (Hitachi Medical Co, Tokyo, Japan) with the use of system subroutines to reconstruct functional images constituting 64 × 64 pixels, each pixel representing 2.5 × 2.5 mm.

Cerebral blood flow (CBF) was determined while the patient was continuously inhaling ^{15}O-labeled carbon dioxide (370 to 555 MBq per minute) through a mask. Measurement of the cerebral metabolic rate of oxygen ($CMRO_2$) and oxygen extraction fraction (OEF) of the brain required continuous inhalation of ^{15}O-labeled oxygen at 740 to 1110 MBq per minute. Scan data were collected for 5 minutes. A single breath of ^{15}O-labeled carbon monoxide (2960 MBq) was used to measure cerebral blood volume (CBV). Calculation of CBF, $CMRO_2$, and OEF was based on the steady-state method,[10] and $CMRO_2$ and OEF were corrected by the CBV.[11]

Positron emission tomography was performed at least 1 month after the latest ischemic event in all patients.

MRI

After PET scanning, MRI (Signa, General Electric, Milwaukee, Wis; 1.5 T) was performed. T_2- and T_1-weighted images were obtained with a spin-echo sequence with a repetition time of 2000 msec and an echo time of 80 msec and a repetition time of 400 msec and an echo time of 20 msec, respectively. Magnetic resonance images were obtained as closely as possible and parallel to the scan plane of the PET images. Slice thickness was 3 mm, with a 2-mm interslice gap.

Data Analysis

Patients with ICO were divided into two subgroups, based on the presence or absence of a high-intensity area in the middle centrum semiovale of the occluded hemisphere on T_2-weighted images. The high-intensity area was a confluent area far from the cerebral cortex and ventricular wall, extending along the dorsolateral aspect of the lateral ventricle (arrow in Fig 1, top left). These abnormalities were usually undetectable on CT and T_1-weighted images. No patients with ICS had this high-intensity area. Patients without this high-intensity area had punctate or patchy, or linear, high-intensity areas in the immediate subcortical or periventricular white matter (Fig 1, middle and

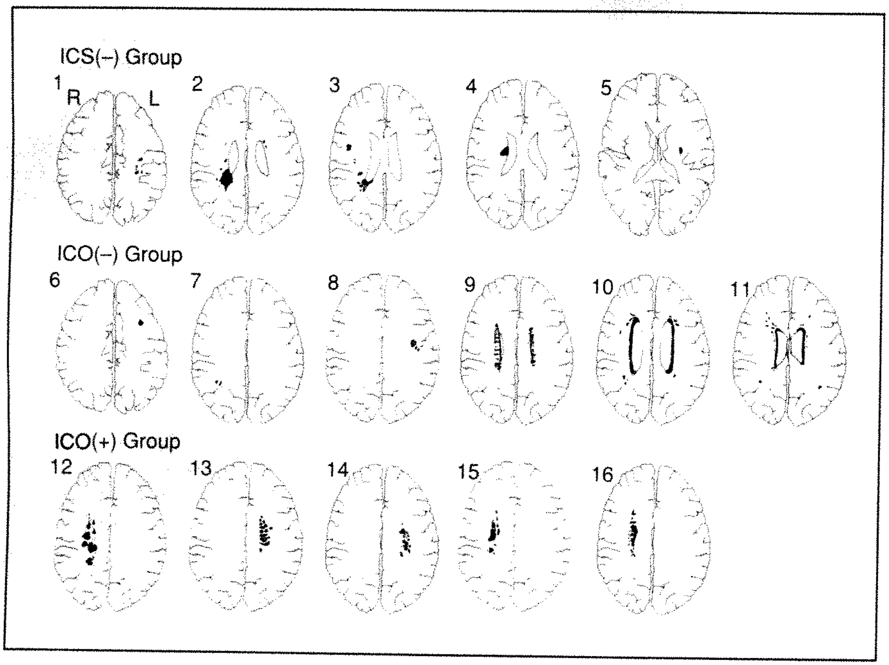

Fig 2.—Distribution of the high-intensity areas on T_2-weighted magnetic resonance images in the three patient groups. Numbers are patient numbers, as listed in Table 1. ICS(–) indicates patients with stenosis without the high-intensity area in the middle centrum semiovale; ICO(–), patients with occlusion without this high-intensity area; and ICO(+), patients with occlusion with this high-intensity area.

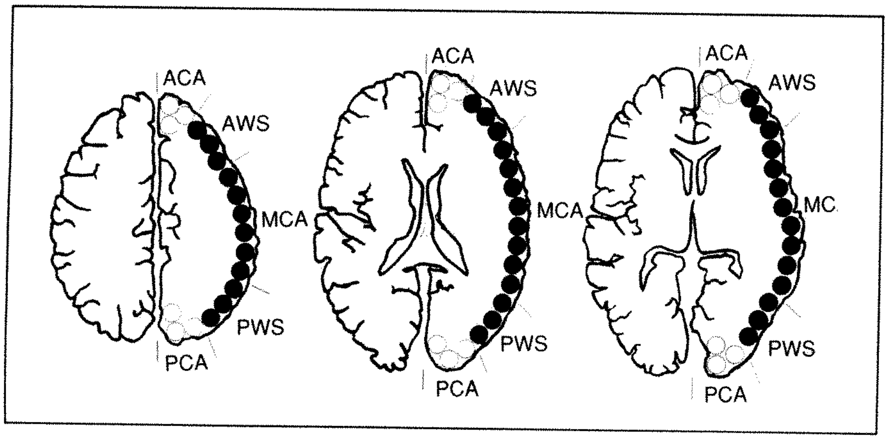

Fig 3.—Three diagrams illustrating circular regions of interest, placed over the cerebral cortex divided into five areas: territories supplied by the anterior cerebral artery (ACA), middle cerebral artery (MCA), and posterior cerebral artery (PCA), as well as the watershed areas between the ACA and MCA (anterior watershed [AWS]) and the MCA and PCA (posterior watershed [PWS]). A hemispheric value was calculated as the average of the MCA, AWS, and PWS in the affected hemisphere (solid circles), weighted by region size.

right). The study patients were then divided into three subgroups: group ICS(–) (n = 5; mean age, 63.2 years) included patients with stenosis without this high-intensity area in the middle centrum semiovale (Fig 1, middle); group ICO(–) (n = 6; mean age, 62.3 years) included patients with occlusion without this high-intensity area (Fig 1, right); and group ICO(+) (n = 5; mean age, 55.2 years) included patients with occlusion with this high-intensity area (Fig 1, left). Clinical and neuroradiologic data on patients in the three groups are summarized in Table 1. Distributions of the high-intensity areas in all cases are illustrated in Fig 2.

We analyzed three tomographic planes—4.0, 6.6, and 8.2 cm above and parallel to the orbitomeatal line. These corresponded to the levels of the basal ganglia and thalamus, the body of the lateral ventricle, and the centrum semiovale. Each image was examined by placing a total of 18 to 20 circular regions of interest, each containing 11 pixels (0.785 cm^2), over the gray matter of the cortex (Fig 3). According to the atlas by Kretschmann and Weinrich,[12] the regions of interest in all three images were included in the distribution of the anterior cerebral artery, MCA, and posterior cerebral artery, as well as the watershed areas between anterior cerebral artery and MCA (anterior watershed) and the MCA and posterior cerebral artery (posterior watershed). A hemispheric value was calculated as the average of the MCA, anterior watershed, and posterior watershed in the affected hemisphere, weighted by region size.

Hemispheric values from the three patient groups were compared with analysis of variance with Bonferroni's t test, with differences yielding $P<.05$ regarded as significant.

RESULTS

The physiologic states of the three patient groups during PET scanning are described in Table 2, including arterial hemoglobin concentration, hematocrit, Pa_{O_2}, Pa_{CO_2}, and mean arterial blood pressure.

Figure 4 shows the hemispheric values for regional CBF, $CMRO_2$, OEF, CBV, and CBF/CBV for each patient in the three groups. Patients with ICO and the high-intensity area in the middle centrum semiovale (ICO[+] group) had significantly ($P<.01$) decreased CBF and CBF/CBV, with significantly ($P<.05$) elevated OEF, compared with the other two groups. The $CMRO_2$ reduction was significant only when compared with the ICS(–) group. A difference in CBF only was present between the ICO(–) and ICS(–) groups.

COMMENT

The high prevalence of subcortical high-intensity areas on T_2-weighted images in the elderly makes its clinical significance obscure.[2] The high intensities include such abnormalities as état criblé, atrophic perivascular demyelination, gliosis, myelin pallor, demyelination, edema, and infarction.[2] In ICO, high-intensity areas on T_2-weighted images are considered to be a result of ischemic changes. Computed tomography and T_1-weighted images do not detect corresponding abnormalities, implying that the high-intensity areas in the T_2-weighed images do not indicate complete infarctions with cavitation but only mild or early ischemic changes. Magnetic resonance imaging is able to detect the abnormalities at an early stage, before severe ischemic damage develops.

Stained or striated hypodense areas in the parietal white matter on CT, mostly in the supraventricular region, have been reported to be a typical finding in cases of stenosis or occlusion of the carotid artery.[3] Another study[5] involving MRI also reported that unilateral high-intensity areas in the deep watershed zone on T_2-weighted images were frequently associated with substantial carotid stenosis, defined as greater than 80%. The watershed in-

Table 2.—Baseline Physiologic Data on Patients in the Three Groups*

Factor	ICS(−)	ICO(−)	ICO(+)
Pa_{CO_2}, mm Hg	43.8 ± 7.0	38.6 ± 10.3	43.0 ± 1.1
Pa_{O_2}, mm Hg	86.0 ± 7.5	86.8 ± 7.0	84.6 ± 7.7
Hematocrit	0.369 ± 0.043	0.378 ± 0.045	0.412 ± 0.021
Hemoglobin, g/L	126 ± 16	126 ± 17	140 ± 21
MABP, mm Hg	99.1 ± 14.1	100.4 ± 12.5	98.7 ± 13.6

*Values are mean ± SD. MABP indicates mean arterial blood pressure. There was no difference among the three groups, which are explained in the text and in Table 1.

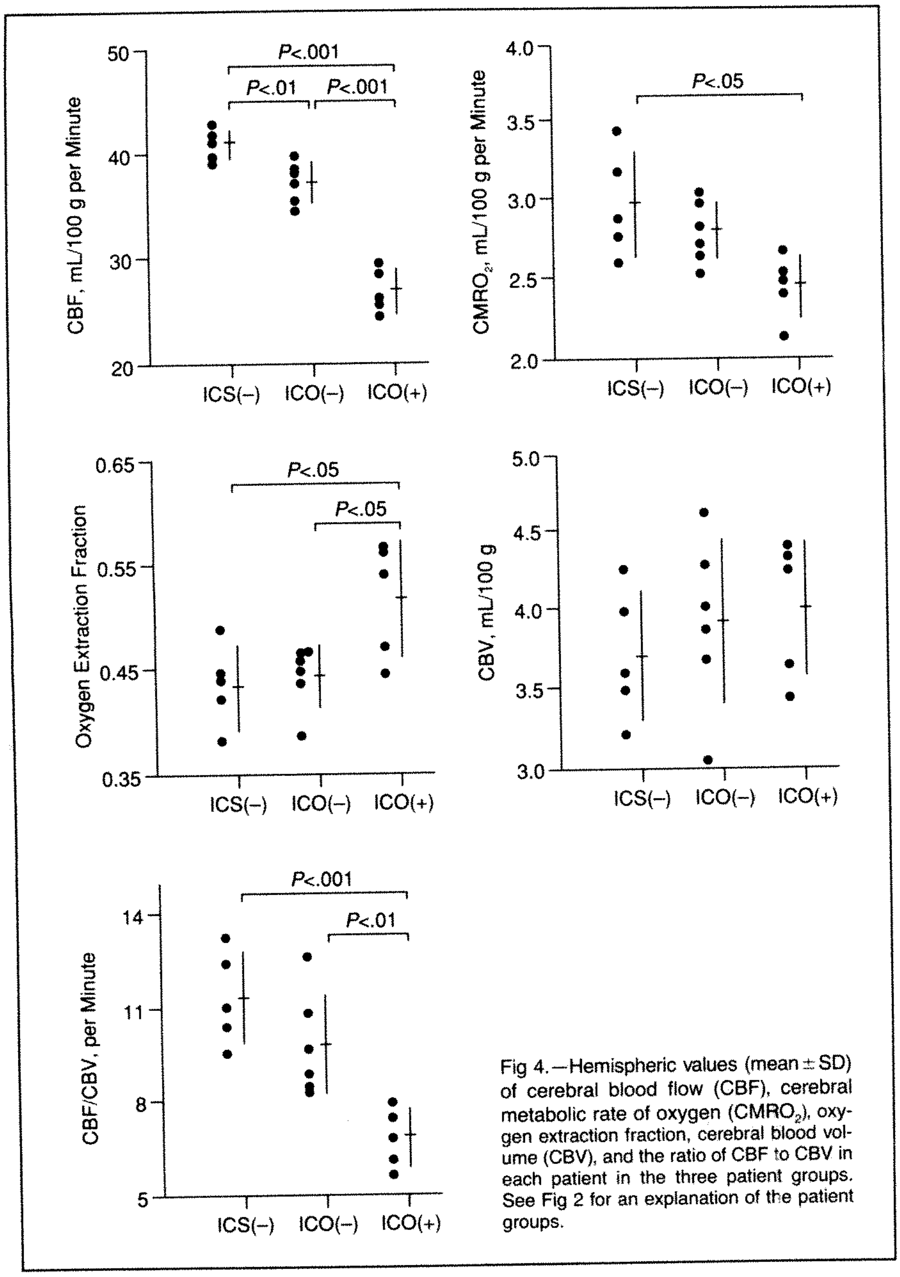

Fig 4.—Hemispheric values (mean ± SD) of cerebral blood flow (CBF), cerebral metabolic rate of oxygen ($CMRO_2$), oxygen extraction fraction, cerebral blood volume (CBV), and the ratio of CBF to CBV in each patient in the three patient groups. See Fig 2 for an explanation of the patient groups.

farctions in ICO are derived from various pathogeneses.[13,14] Among them, deep watershed infarction has been believed to be hemodynamic.[4,6,8,15] Internal carotid artery occlusion with adequate anterior circle of Willis anastomosis, such as in our patients, has often been associated with this type of hemodynamically induced infarction.[16] The middle centrum semiovale is a watershed zone supplied by the distal intraparenchymal penetrating arterioles[7,8] and is the most distal white matter area perfused by collateral vessel circulation through the anterior portion of the circle of Willis after ICO. Hypoperfusion from ICO generates ischemic changes in this area at an early stage. We reported that the confluent high-intensity area on T_2-weighted images in the middle centrum semiovale contained increased CBV.[17] This finding indicates that this high-intensity area that is susceptible to a reduction in perfusion pressure has prominent compensatory vasodilatation.[18] We also showed in this study that patients with this high-intensity area had less hemodynamic reserve, decreased CBF, increased OEF, and decreased CBF/CBV ratio in the cerebral cortex compared with those without it. Minor cerebral perfusion pressure change would elicit more devastating CBF reduction, resulting in ischemic changes in such less reserved hemisphere than normally perfused brain.[18,19] This high-intensity area on MRI is a serious sign of a deterioration of hemodynamic state in ICO with good collateral vessel circulation through the anterior portion of the circle of Willis.

Few studies have attempted to correlate white matter lesions on MRI with CBF and metabolism.[20-24] In carotid artery diseases with various degrees of white matter lesions, only multiple large or confluent white matter lesions in any location are accompanied by reduced cortical CBF, with no relationship between the degree of the white matter lesions and the severity of the hypoperfusion.[22] White matter lesions, without taking into account their topography, are nonspecific findings and do not relate to the hemodynamic change resulting from carotid artery disease. We should note whether high-intensity areas exist in the region vulnerable or not vulnerable to decreased perfusion.

CONCLUSION

The confluent high-intensity area on T_2-weighted images in the middle centrum semiovale indicates hemodynamic compromise in ICO with good collateral vessel circulation through the anterior portion of the circle of Willis. Detection of this abnormality necessitates strict control of systemic hemodynamic factors, such as systemic blood pressure and blood viscosity,[25,26] and further investigation of the hemodynamic state of general circulation. Ischemic changes resulting from hypoperfusion may, in their early stages, produce only subtle, subjective symptoms but be easily detectable with MRI. Therefore, MRI is a useful diagnostic tool to identify patients at risk for hemodynamic ischemia before the development of major neurologic deficits or infarction.

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References

1. Brant-Zawadzki M. MR imaging of the brain. *Radiology*. 1988;166:1-10.
2. Drayer BP. Imaging of the aging brain, I: normal findings. *Radiology*. 1988;166:785-796.
3. Wodarz R. Watershed infarctions and computed tomography: a topographical study in cases with stenosis or occlusion of the carotid artery. *Neuroradiology*. 1980;19:245-248.
4. Ringelstein EB, Zeumer H, Angelou D. The pathogenesis of strokes from internal carotid artery occlusion: diagnostic and therapeutical implications. *Stroke*. 1983;14:867-875.
5. Kinkel PR. Nuclear magnetic resonance imaging in clinical neurology. In: Joynt RJ, eds. *Clinical Neurology*. Philadelphia, Pa: JB Lippincott; 1989;1:chap 4.
6. Waterson JA, Brown MM, Butler P, Swash M. Small deep cerebral infarcts associated with occlusive internal carotid artery disease: a hemodynamic phenomenon? *Arch Neurol*. 1990;47:953-957.
7. Zulch KJ, Hossmann V. Patterns of cerebral infarctions. In: Vinken PJ, Bruyn GW, Klawans HL, Toole JF, eds. *Handbook of Clinical Neurology: Vascular Disease*. Amsterdam, the Netherlands: Elsevier Science Publishers; 1988;53:175-198.
8. Moody DM, Bell MA, Challa VR. Features of the cerebral vascular pattern that predict vulnerability to perfusion or oxygenation deficiency: an anatomic study. *AJNR*. 1990;11:431-439.
9. Senda M, Tamaki N, Yonekura Y, et al. Performance characteristics of Positlogica III: a whole-body positron emission tomograph. *J Comput Assist Tomogr*. 1985;9:940-946.
10. Frackowiak RSJ, Lenzi GL, Jones T, Heather JD. Quantitative measurement of regional cerebral blood flow and oxygen metabolism in man using ^{15}O and positron emission tomography: theory, procedure, and normal values. *J Comput Assist Tomogr*. 1980;4:727-736.
11. Lammertsma AA, Jones T. Correction for the presence of intravascular oxygen-15 in the steady state technique for measuring regional oxygen extraction ratio in the brain, I: description of the method. *J Cereb Blood Flow Metab*. 1983;3:416-424.
12. Kretschmann HJ, Weinrich W. *Neuroanatomie der kraniellen Computertomographie: Grundlagen und klinische Anwendung*. Stuttgart, West Germany: George Thieme Verlag; 1984:72.
13. Torvik A. The pathogenesis of watershed infarcts in the brain. *Stroke*. 1984;15:221-223.
14. Bogousslavsky J, Regli FA. Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications. *Ann Neurol*. 1986;20:346-350.
15. Lee S, Terashi A. Progressive periventricular hyperintensity on MR imaging. *AJNR*. 1989;152:654-655.
16. Rodda RA, Path FRC. The arterial patterns associated with internal carotid disease and cerebral infarcts. *Stroke*. 1986;17:69-75.
17. Yamauchi H, Fukuyama H, Harada K, et al. White matter hyperintensities may correspond to areas of increased blood volume: correlative MR and PET observations. *J Comput Assist Tomogr*. 1990;14:905-908.
18. Powers WJ, Raichle ME. Positron emission tomography and its application to the study of cerebrovascular disease in man. *Stroke*. 1985;16:361-376.
19. Gibbs JM, Wise RJS, Leenders KL, Jones T. Evaluation of cerebral perfusion reserve in patients with carotid artery occlusion. *Lancet*. 1984;1:310-314.
20. Fazekas F, Niederkorn K, Schmidt R, et al. White matter signal abnormalities in normal individuals: correlation with carotid ultrasonography, cerebral blood flow measurements, and cerebrovascular risk factors. *Stroke*. 1988;19:1285-1288.
21. Delpla P, Meyer R, Zatorre R, et al. Metabolic and neuropsychological correlates of periventricular lucencies. *J Cereb Blood Flow Metab*. 1989;9(suppl 1):569.
22. Herholz K, Heindel W, Rackl A, et al. Regional cerebral blood flow in patients with leukoaraiosis and atherosclerotic carotid artery disease. *Arch Neurol*. 1990;47:392-396.
23. Kobari M, Meyer JS, Ichijo M, Oravez WT. Leukoaraiosis: correlation of MR and CT findings with blood flow, atrophy, and cognition. *AJNR*. 1990;11:273-281.
24. Meguro K, Hatazawa J, Yamaguchi T, et al. Cerebral circulation and oxygen metabolism associated with subclinical periventricular hyperintensity as shown by magnetic resonance imaging. *Ann Neurol*. 1990;28:378-383.
25. Bogousslavsky J, Regli FA. Borderzone infarctions distal to internal carotid artery occlusion: prognostic implications. *Ann Neurol*. 1986;20:346-350.
26. Meyer JS, Judd BW, Tawaklna T, Rogers RL, Mortel KF. Improved cognition after control of risk factors for multi-infarct dementia. *JAMA*. 1986;256:2203-2209.

Automatic Memory Processes in Patients With Multiple Sclerosis

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• To better understand the nature of the memory deficit in patients with multiple sclerosis, we designed a study to compare automatic vs effortful memory processes. Forty-one patients with definite multiple sclerosis and 45 demographically matched normal control subjects were administered two tasks designed to assess both automatic (monitoring frequency and modality) and effortful (free and cued-recall) processing. Results indicated that patients with multiple sclerosis, as expected, were significantly impaired on memory measures requiring effort, but performed normally on automatic measures. Performance on the memory indexes did not correlate with self-reported depression. The implications of these findings for delineating the locus of the memory impairment in multiple sclerosis is discussed.

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Recent neuropsychologic studies have shown that approximately 50% of patients with multiple sclerosis (MS) exhibit disorders of memory (for a recent review of this literature, see Grafman et al[1]). The most common form of memory loss is characterized by an impairment in episodic memory, defined as an inability to retrieve daily events that occur at a specific time and place.[2-7] Only rarely do MS patients experience difficulty with semantic memory, ie, retrieving names, facts, and concepts.[8,9] This distinction between episodic and semantic memory is a popular one, which has been intensively studied in normal and impaired populations.[10-12]

Another useful distinction in characterizing memory processes contrasts effortful vs automatic cognitive operations.[13,14] *Effortful* operations usually refer to explicit search and strategy procedures used to encode and then recall or recognize previously presented material. *Automatic* operations, in contrast, tend to require less focused attention and are involved in encoding and retrieving the (task-defined) less salient aspects of a stimulus.[15-17] Hasher and Zacks[13] described a variety of tasks that fulfilled their criterion for measuring automaticity and included tests of frequency (eg, how often a stimulus appeared[18]) and stimulus modality (eg, recall of whether an item was originally shown as a picture or word) monitoring. Automatic operations appeared to demand less sustained concentration and fewer cognitive resources.[16,17] Thus, items automatically processed should be equally recalled under intentional and incidental encoding conditions. Furthermore, practice in coding frequency or modality would also be expected to have little effect on effortful recall of item frequency or modality.[19] In addition, attention to other aspects of a task should not detract from automatic processing.[14]

One test of the functional independence of automatic memory operations would be to study abnormal populations on tasks requiring both automatic and effortful operations.[20,21] Because an aspect of the way in which people remember events in episodic memory (eg, events occurring while eating dinner at a new restaurant) is by "automatically" recording the less salient or attended-to properties of episodes (eg, how long it took to eat dessert) in parallel with "effortful" processing during the episode (eg, remembering where one ate for dinner), it might be expected that both processes would be adversely affected by central nervous system diseases such as MS that affect retrieval of episodic memories. In addition, because automatic processing should be resistant to changes in effort or motivation,[22] it might be a particularly sensitive measure (compared with other standard effortful memory measures such as story recall or word list learning) to use in separating out the effects of depression from the more direct effects of MS on memory. The effort required to encode information using cognitive strategies may be constrained by certain symptoms found in depressed patients, such as lack of energy or amotivation.

In the experiments reported below, we utilized two tasks designed to evaluate automatic and effortful processing. One task evaluated subject sensitivity to the frequency of stimulus presentation using both frequency monitoring and free-recall measures, while the other task evaluated paired-associate learning using both stimulus modality monitoring and free and cued-recall measures. We predicted that MS patients would not be impaired on automatic processing measures, but that their performance on the effortful measures would distinguish them from control subjects.

SUBJECTS AND METHODS

Subjects

Patients with MS (n = 41) and matched control subjects (n = 45) were included in this study. The MS patients who participated in this study were recruited randomly from a membership listing compiled by a local MS society. Medical records were reviewed to determine the basis for the diagnosis of MS. In addition, all patients underwent a neurologic examination and magnetic resonance imaging as part of the present study. Diagnosis was established by the results of neurologic and neuro-ophthalmologic examination, evoked potentials, cerebrospinal fluid analysis, and brain imaging. As a result of the recruitment method, all but two (4.9%) patients were in remission at the time of the evaluation. All patients met the criteria for clinically or laboratory-supported definite MS, as determined by the criteria of Poser et al.[23] Patients with a history of alcohol or drug abuse or nervous system disorders other than MS were excluded. Physical disability was rated on the 10-point Expanded Disability Status Scale.[24] Eight (19.5%) patients were taking potentially psychoactive medications at the time of the evaluation. No MS patient rated as clinically depressed on the Zung Depression Scale (see below) had received electroconvulsive therapy.

Control subjects were also screened for evidence of cognitive dysfunction, neurologic disorders, alcohol or drug abuse, or positive psychiatric history and were excluded if they had a first-degree relative with either major affective disorder or dementia. Subjects were matched as closely as possible for sex, age, and education level (Table). Both MS patients and control subjects were paid for their participation in this study.

Both groups were administered the Mini-Mental State[25] dementia examination, and the Zung Self-Rating Depression Scale.[26] The MS group reported significantly more

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symptoms of depression than did control subjects (Table). In addition, there was a marginally significant group difference on the Mini-Mental State examination.

Testing

Control subjects and MS patients were administered all tests during the same testing session at the Medical College of Wisconsin, Milwaukee. Test administration was counterbalanced within groups.

Frequency Monitoring.—We used a version of the Hasher and Zacks[14] Frequency Monitoring Task. A list of 90 words was read to the subjects at a rate of one word every 3 seconds. Within the list, some words were presented once, others twice, three times, and up to seven times. Subjects were asked to listen carefully and try to remember the words. After a brief interval at the end of the testing session, subjects were asked to recall all the words that they could remember from the list (free recall). Following another brief delay, subjects were told that they would be presented with a set of words from the list (they were also told that some of the words had not been presented) and were asked to judge how often the word had appeared on the previous list (frequency monitoring). Scoring included total number of words recalled in the free-recall condition, number of words freely recalled from each frequency category, and a subject estimate of the number of times words from each frequency category appeared on the original list. In addition, we subtracted the estimated mean frequency of words that actually appeared from one to three times on the list from words that appeared four to seven times to obtain an index of frequency monitoring. The numbers of words for each actual frequency (AF) category were presented to subjects in the estimation part of the task as follows: AF0 = 3; AF1 = 4; AF2 = 5; AF3 = 6; AF4 = 6; AF5 = 3; AF6 = 2; and AF7 = 1.

Paired-Associate Learning Test.—Subjects were shown 32 pairs of stimuli. Eight of the pairs were concrete, imaginable words, eight of the pairs were pictures (line drawings of objects), eight pairs were composed of a word-picture combination, and the last eight pairs were of the picture-word form. Half the pairs were made up of related items; half were unrelated. After viewing all the pairs, subjects were asked to freely recall all of the items that were presented. Next, subjects were shown a cue (the initial item of a pair) and asked to recall the associate. Finally, subjects were told that they would hear the names of all items that were on the test and would be asked to say whether they were originally presented as a picture or as a word. Variables of interest include free and cued recall and modality of presentation. Remembering whether an item was presented as a word or as a picture was considered an incidental learning (ie, automatic processing) condition. One MS patient did not take this test.

The key variables of interest were the effects due to group and those due to type of cognitive processing operation (ie, effortful vs automatic). *Effortful operations* in both the Paired-Associate and Hasher Frequency Estimation tasks were considered the free and cued-recall measures. *Automatic operations* were represented by the frequency estimation and modality monitoring measures. A more complete description of the tasks used here and their relationship to each other can be found in a study by Weingartner et al.[27] Statistical comparisons used analysis of variance for main effects and Tukey-B tests for group comparisons. Correlations were completed using Pearson product correlation coefficients. All data are reported as means ± SDs.

Subject Table

	Patients With Multiple Sclerosis (n = 41)	Normal Control Subjects (n = 45)
Age, y	47.8 (7.9)	47.0 (8.3)
Education, y	13.6 (2.6)	14.2 (2.3)
Sex, M/F	11/30	5/40
Zung Depression Scale score	40.1 (9.8)	33.7 (9.9)†
Mini-Mental State Examination score	28.7 (1.6)	29.3 (1.1)*
Expanded Disability Status Scale score	4.57 (2.4)	. . .
Duration of symptoms, y	16.1 (7.58)	. . .

*$P<.06$.
†$P<.01$.

RESULTS

Effortful Processing: Free and Cued Recall

We first compared overall free recall on the Hasher Frequency Monitoring Task and found a significant between-group difference ($F[1,84]=7.41$; $P<.008$). In addition, we found an expected significant main effect for frequency ($F[3,252]=59.48$; $P<.0001$) but a nonsignificant group × frequency interaction ($P>.10$). Control subjects recalled significantly more words than did MS patients, but both groups benefited in free recall by having words repeated during stimulus presentation (Fig 1). Results from the free-recall portion of the Paired-Associate Test (Fig 2) again revealed that control subjects recalled more items than did MS patients ($t[83]=-4.20$; $P<.0001$). Under cued-recall conditions (Figs 3 and 4), there was a significant between-group effect for the related *and* unrelated pairs comparison ($F[1,83]=9.64$; $P<.003$) as well as for all the picture-word pair combinations ($F[1,83]=9.64$; $P<.003$). Both control subjects and MS patients remembered more related than unrelated pairs ($F[1,83]=591.37$; $P<.0001$) and more pairs when the item cue was a picture ($F[3,249]=16.75$; $P<.0001$). None of the group by condition interactions were significant for cued-recall processing.

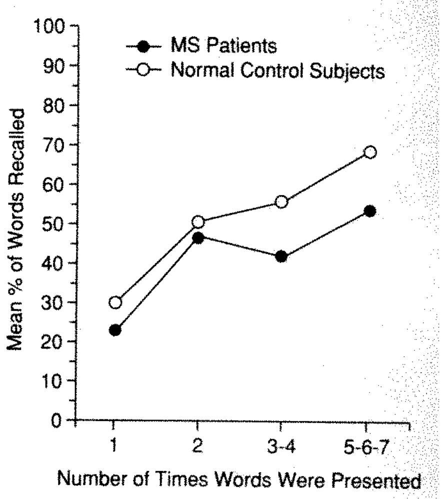

Fig 1.—Hasher Frequency Discrimination Task: free recall of words as a function of how frequently a word had been presented. MS indicates multiple sclerosis.

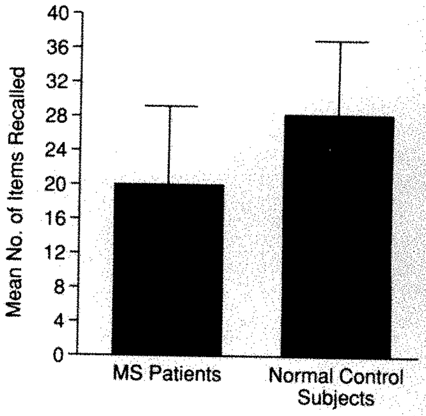

Fig 2.—Paired-Associate Test: free recall. MS indicates multiple sclerosis.

Automatic Processing: Frequency and Modality Monitoring

When asked to estimate the frequency with which a word appeared on the Hasher Frequency Monitoring Task word list (Fig 5), both control subjects and MS patients demonstrated that they were sensitive to increasing frequency of stimulus presentation ($F[7,588]=154.93$; $P<.0001$). There were no overall between-group differences in frequency estimation ($P>.10$), although a significant group by frequency interaction effect ($F[7,588]=4.50$; $P<.001$) was found, indicating that MS patients tend to make judgments that underestimate frequently presented words and overestimate words that were presented infrequently or even not at all. As far as modality monitoring on the Paired-Associate Test was concerned (Fig 6), there were no significant between-group differences.

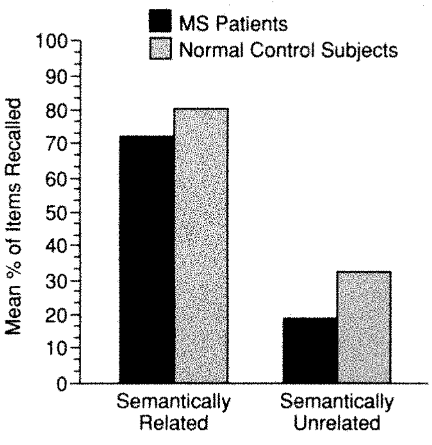

Fig 3.—Paired-Associate Test: cued recall as a function of semantic relatedness. MS indicates multiple sclerosis.

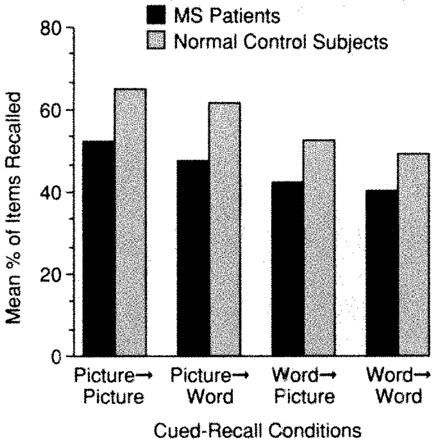

Fig 4.—Paired-Associate Test: cued recall as a function of stimulus modality pairing. MS indicates multiple sclerosis.

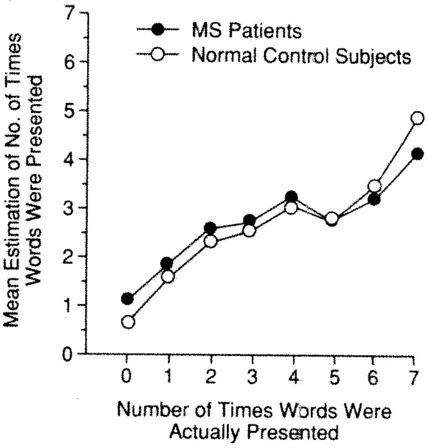

Fig 5.—Hasher Frequency Discrimination Task: estimations of the number of times a word had been presented on the study list (automatic processing). MS indicates multiple sclerosis.

Other Results

There were no group differences on the number of intrusions for either test. For the MS patients, the free-recall measures from both tests were significantly correlated ($r=.58$, $P<.0001$), as were the two automatic memory measures (frequency/modality monitoring; $r=.45$, $P<.005$). In contrast, for the control subjects, the free-recall measures were significantly correlated ($r=.63$, $P<.0001$), but the frequency/modality measures were not ($r=.26$, $P>.05$). This might be due to a ceiling effect for the control subjects on the modality monitoring measure.

There were no significant ($P<.01$) correlations between the automatic and effortful memory measures and depression (Zung scale), physical disability (Expanded Disability Status Scale), duration of symptoms, or education.

COMMENT

Our results indicate that MS patients, like control subjects, are sensitive to the less attended aspects of stimulus processing such that they are able to retrieve incidental properties (ie, the modality of a stimulus or its frequency of presentation) of a stimulus that elicited predominantly semantic processing. On the frequency monitoring measure, MS patients tended to underestimate frequently presented items and overestimate rarely presented items, suggesting that they adapted a conservative scaling bias. As expected, the MS patients had some difficulty on effort-demanding memory measures such as free and cued-recall processings. However, their performance on cued-recall processing was as sensitive as that of the control subjects to the conditions of relatedness and type of cue. This finding of effortful memory deficit is rather nonspecific because it occurs in almost all patients with brain disease or serious psychiatric disorder and it has been observed across almost all studies of MS. Our results also indicated that level of depression played no role in the effortful memory deficit of patients with MS.

Why do MS patients succeed on these measures of automatic processing despite problems in effortful processing? Hirst and Volpe[17] described the performance of amnesics on measures of automatic processing and reported that adequate performance on such measures required relatively intact *effortful* processing. Yet Beatty et al[28] and Rao et al[29] have found that MS patients who also have poor effortful memory as seen on free and cued-recall tasks do well on automatic and implicit memory tasks. Perhaps so-called automatic operations basically represent another form of implicit priming, which appears relatively intact in MS patients. In this case, one possible explanation for the good performance of MS patients on automatic processing measures despite impaired effortful memory is that their memory deficit may primarily involve the conscious, effortful *strategic* aspects of searching long-term memory. Because automatic and incidental memory processes by their very definition should be independent of conscious, effortful strategic *search*, but still require intact memory encoding and *storage*, they could be spared in MS patients. This would suggest that the efficiency of "automatic processes" may also depend on having adequate resources to process information in parallel. Depending on task instructions, some aspects of information (eg, meaningfulness) are processed using focused attention; other aspects of information (eg, phonological information) may be processed outside the window of focused attention. This passive parallel processing of information also has to time-share resources with concurrent active processing such as overt verbal rehearsal. What we are calling the passive processing of information is similar to even more covert activation processes such as those used in implicit memory tasks. Thus, adequate automatic processing should depend more on the passive strengthening of previous semantic representations and their associational links, relative to the effort made in strategic or controlled memory search.

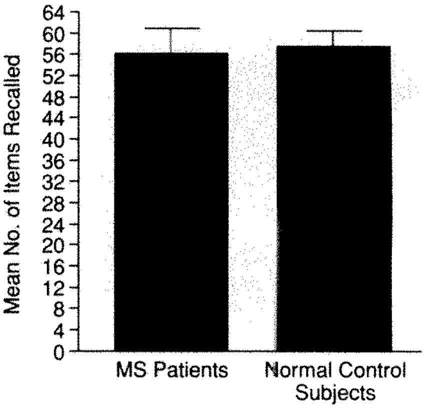

Fig 6.—Paired-Associate Test: incidental recall of whether a test item was originally presented as a picture or word (automatic processing). MS indicates multiple sclerosis.

Therefore, it follows that if certain representations and their associational links are spared in selected central nervous system disorders like MS, then their "slavish" specific automatic processes may be spared too. This hypothesis would be better tested in patients with unilateral cortical lesions rather than MS. For example, an effortful measure such as remembering words might be impaired in left-hemisphere patients, but incidentally identifying the location where words were presented in a grid (a candidate for an automatic measure in this scenerio) might be spared (if "right-hemisphere spatial location processes" remained intact).

An alternative explanation for intact automatic processing in light of impaired effortful processing in MS patients is that they may have difficulty coding verbal information within working memory.[4] In particular, there is some evidence that MS patients have problems in temporarily storing phonological information within a rehearsal loop for later processing. In this model, automatic processing requires intact semantic activation processes that can operate independently of working memory (and that appear intact in MS), whereas effortful structurally based processes (eg, covert rehearsal of verbal-phonological information) depend on activating buffers within working memory (that appears affected by MS).

Processes such as frequency and modality estimation will rarely meet all the strict criteria for automaticity established by Hasher and Zacks.[13,14] Some researchers have described these so-called automatic processes as requiring *relatively* less focused attention than effortful structural or semantic categorization/identification but lying on a *continuum* of attention and effort during encoding.[30,31] Thus, by manipulating encoding strategy and attentional effort, accuracy in estimating frequency or the modality of a stimulus can be degraded.[32,33] Neither of those manipulations were done in the present study.

As noted above, the evidence from the performance of the MS patients whom we studied suggests that simply a decrease in effortful processing (reflected in *particularly* impaired free recall) will not correspond to impaired accuracy in modality or frequency estimation. However, even in the case of patients with dementia of the Alzheimer's type who demonstrate impaired frequency and modality estimation along with impaired effortful processing, there was no significant rank-order correlation between free recall and accuracy in frequency or modality estimation.[20]

Thus, our findings would argue for at least a partial independence of the cognitive processes required for frequency and modality monitoring from those required for effortful encoding and retrieval. Automatic processes bear some resemblance to implicit memory processes that may depend on intact cortical structures, whereas effortful or explicit memory processes may depend more on subcortical structures such as the hippocampus. Since plaques in MS tend to appear in subcortical regions, it should be expected that effortful memory processes are most at risk in MS.

Other studies[28,29] have demonstrated that MS patients perform better on tasks not requiring declarative memory such as procedural learning and priming and have access to semantic knowledge. In addition, MS patients tend to perform much better on recognition vs recall measures.[34] Measures of automatic processing can now be added to the list of measures on which MS patients perform normally. Nevertheless, most measures requiring free or cued-recall processing appear disturbed to various degrees in MS patients. In the future, we plan to conduct follow-up studies of MS patients employing conditions such as rate of information presentation, phonological and information load, interference, and type of retrieval required to better identify the locus of the memory deficit.

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References

1. Grafman J, Rao SM, Litvan I. Disorders of memory. In: Rao SM, ed. *Neurobehavioral Aspects of Multiple Sclerosis.* New York, NY: Oxford University Press; 1990:102-117.

2. Beatty WW, Goodkin DE, Monson N, Beatty PA, Hertsgaard D. Anterograde and retrograde amnesia in patients with chronic progressive multiple sclerosis. *Arch Neurol.* 1988;45:611-619.

3. Grant I, McDonald WI, Trimble MR, Smith E, Reed R. Deficient learning and memory in early and middle phases of multiple sclerosis. *J Neurol Neurosurg Psychiatry.* 1984;47:250-255.

4. Litvan I, Grafman J, Vendrell P, et al. Multiple memory deficits in patients with multiple sclerosis: exploring the working memory system. *Arch Neurol.* 1988;45:607-610.

5. Minden SL, Moes EJ, Orav J, Kaplan E, Reich P. Memory impairment in multiple sclerosis. *J Clin Exp Neuropsychol.* 1990;12:566-586.

6. Rao SM, Hammeke TA, McQuillen MP, Khatri BO, Lloyd D. Memory disturbance in chronic progressive multiple sclerosis. *Arch Neurol.* 1984;41:625-631.

7. Rao SM, Leo GJ, St Aubin-Faubert P. On the nature of memory disturbance in multiple sclerosis. *J Clin Exp Neuropsychol.* 1989;11:699-712.

8. Beatty WW, Goodkin DE, Monson N, Beatty PA. Cognitive disturbances in patients with relapsing remitting multiple sclerosis. *Arch Neurol.* 1989;46:1113-1119.

9. Filley CM, Heaton RK, Nelson LM, Burks JS, Franklin GM. A comparison of dementia in Alzheimer's disease and multiple sclerosis. *Arch Neurol.* 1989;46:157-161.

10. Martin A, Fedio P. Word production and comprehension in Alzheimer's disease: the breakdown of semantic knowledge. *Brain Lang.* 1983;19:121-141.

11. Weingartner H, Grafman J, Boutelle W, Kaye W, Martin PR. Forms of memory failure. *Science.* 1983;221:380-382.

12. Cermak LS. The episodic-semantic distinction in amnesia. In: Squire LR, Butters N, eds. *Neuropsychology of Memory.* New York, NY: The Guilford Press; 1984:55-62.

13. Hasher L, Zacks RT. Automatic and effortful process in memory. *J Exp Psychol [Gen].* 1979;108:356-388.

14. Hasher L, Zacks RT. Automatic processing of fundamental information: the case of frequency of occurrence. *Am Psychol.* 1984;39:1372-1388.

15. Hoffman JE. Event-related potentials and automatic and controlled processes. *Biol Psychol.* 1988;20:163-184.

16. Hirst W, Volpe BT. Temporal order judgments with amnesia. *Brain Cogn.* 1982;1:294-306.

17. Hirst W, Volpe BT. Automatic and effortful encoding in amnesia. In: Gazzaniga MS, ed. *Handbook of Cognitive Neuroscience.* New York, NY: Plenum Press; 1984:369-386.

18. Jackson JL. Is the processing of temporal information automatic or controlled. In: Michon JA, Jackson JL, eds. *Time, Mind, and Behavior.* New York, NY: Springer-Verlag NY Inc; 1985:179-190.

19. Jacoby LL. Incidental versus intentional retrieval: remembering and awareness as separate issues. In: Squire LR, Butters N, eds. *Neuropsychology of Memory.* New York, NY: The Guilford Press; 1984:145-156.

20. Grafman J, Weingartner H, Lawlor B, Mellow AM, Thompsen-Putnam K, Sunderland T. Automatic memory processes in patients with dementia-Alzheimer's type (DAT). *Cortex.* 1990; 26:361-371.

21. Levin HS, Goldstein FC, High WM, Williams D. Automatic and effortful processing after severe closed head injury. *Brain Cogn.* 1988;7:283-297.

22. Kahneman D. *Attention and Effort.* Englewood Cliffs, NJ: Prentice-Hall International Inc; 1973.

23. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis. *Ann Neurol.* 1983;13:227-231.

24. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale. *Neurology.* 1983;33:1444-1452.

25. Folstein MF, Folstein SE, McHugh PR. 'Mini-Mental State': a practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res.* 1975;12:189-198.

26. Zung WWK. A self-rating depression scale. *Arch Gen Psychiatry.* 1965;12:63-70.

27. Weingartner H, Burns S, Diebel R, LeWitt PA. Cognitive impairments in Parkinson's disease: distinguishing between effort-demanding and automatic cognitive processes. *Psychiatry Res.* 1984;11:223-235.

28. Beatty WW, Goodkin DE, Monson N, Beatty PA. Implicity learning in patients with chronic progressive multiple sclerosis. *Int J Clin Neuropsychol.* In press.

29. Rao SM, Mittenberg W, DiGulio D, Leo GJ. Implicit memory in multiple sclerosis. In press.

30. Naveh-Benjamin M, Jonides J. On the automaticity of frequency coding: effects of competing task load, encoding strategy, and intention. *J Exp Psychol [Learn Mem Cogn].* 1986;12:378-386.

31. Jonides J, Naveh-Benjamin M. Estimating frequency of occurrence. *J Exp Psychol [Learn Mem Cogn].* 1987;13:230-240.

32. Birnbaum IM, Taylor TH, Johnson MK, Raye CL. Is event frequency encoded automatically? The case of alcohol intoxication. *J Exp Psychol [Learn Mem Cogn].* 1987;13:251-258.

33. Sanders RE, Gonzalez EG, Murphy MD, Liddle CL, Vitina JR. Frequency of occurrence and the criteria for automatic processing. *J Exp Psychol [Learn Mem Cogn].* 1987;12:241-250.

34. Rao SM. Neuropsychology of multiple sclerosis: a critical review. *J Clin Exp Neuropsychol.* 1986;8:503-542.

Importance of Intrathecal Synthesis of IgD in Multiple Sclerosis

A Combined Clinical, Immunologic, and Magnetic Resonance Imaging Study

Mohammad K. Sharief, MB, ChB, MPhil, Romain Hentges, MD

• There is increasing evidence that soluble IgD has a certain role in the humoral immune response within the central nervous system. We report herein the results of a combined clinical, magnetic resonance imaging, and immunopathologic study to determine the clinical importance of intrathecal IgD synthesis. Intrathecal synthesis of IgD (detected through the calculation of index values) was studied in 64 patients with multiple sclerosis and in 50 neurologic control patients and normal subjects. Locally secreted IgD was detected in 30% of patients with clinically active multiple sclerosis, including two in whom magnetic resonance images of brain and spinal cord were normal and who had no evidence of intrathecal IgG synthesis. No intrathecal IgD production was detected in patients with clinically stable multiple sclerosis or those suffering from chronic progressive multiple sclerosis, while it significantly correlated with the interval from the last relapse and with the total duration of the disease process in patients with relapsing, remitting multiple sclerosis. Intrathecal IgD synthesis also correlated with the degree of cerebrospinal fluid pleocytosis and with the presence of free κ and λ light chain bands in cerebrospinal fluid. Present results supplement and expand earlier data and suggest that intrathecally secreted IgD is a putatively important part of the immune response in clinically active relapsing, remitting multiple sclerosis.

(*Arch Neurol.* 1991;48:1076-1079)

IgD is expressed on greater than 90% of mature B lymphocytes[1] and is considered to be an indicator of B-cell maturity. Evidence suggests that soluble (ie, secreted) IgD has a legitimate antibody function[2] that makes it particularly helpful in the study of early immune response, including that of the central nervous system.[3] The level of soluble IgD in cerebrospinal fluid (CSF), however, is extremely low compared with levels of IgG, IgA, and IgM and is technically difficult to detect. Thus, although IgD levels in the normal reference population[4] and in various neurologic disorders[5] have been previously described, intrathecal production of IgD, through the calculation of the IgD index, has only recently been reported.[6,7]

So far, the clinical importance of intrathecal IgD synthesis in patients with multiple sclerosis (MS) has not been evaluated. Similarly, immunopathologic correlation of this finding with other CSF features of MS has not been properly investigated. We report herein a combined study in which we evaluated the relationship of intrathecal production of IgD to both clinical and paraclinical manifestations of MS.

PATIENTS AND METHODS

Patients

Paired CSF and serum samples from 64 patients with clinically definite MS[8] were utilized in our study (Table 1). Patients with clinically active disease had not received immunomodulatory treatment within 9 months of CSF collection. Patients with chronic progressive MS had progressed steadily since the onset of their disease,[9] while patients with clinically stable MS had relapsing, remitting disease and were in clinical remission at the time of the lumbar puncture.

The neurologic control group (Table 1) contained patients with various neurologic disorders in whom immunologic mechanisms were unlikely to participate. This control group included patients with Alzheimer's disease (four patients), benign intracranial hypertension (four patients), cervical spondylosis without myelopathy (three patients), epilepsy (three patients), amyotrophic lateral sclerosis (five patients), cerebrovascular diseases (four patients), Parkinson's disease (four patients), and peripheral neuropathy (five patients). Normal control subjects presented with tension headache or neurosis and detailed clinical and laboratory investigations showed no sign of neurologic disease. These normal subjects were included to calculate normal reference ranges of IgD and IgG in CSF and serum samples.

Preparation of Samples

Paired CSF and serum samples were collected simultaneously, and 1000 kallikrein inactivator units of affinity purified protease inhibitor, aprotinin (A4529, Sigma Chemical Company, St Louis, Mo), were immediately added to each millimeter of test samples to prevent IgD degradation. Cerebrospinal fluid samples were selected to exclude xanthochromic specimens and specimens containing more than one erythrocyte per field at the time of collection. The CSF samples were centrifuged for 20 minutes at 200*g*, and then both CSF and serum specimens were frozen in aliquots at −70°C immediately after centrifugation and thawed just before use.

Quantitative Determinations

IgD concentration in CSF and serum samples was determined by enzyme-linked immunosorbent assay, as recently described.[7] In brief, wells of polyvinyl chloride microtiter plates were coated with 100 mL of 1:4000 dilution of anti-human δ chain antiserum (A-093, Dakopatts, Dako, Copenhagen, Denmark), blocked by 2% bovine serum albumin and 0.1% polysorbate (Tween, BDH Ltd, Poole, England) in phosphate-buffered saline, then incubated with test samples. After overnight incubation, IgD reactivity in the test samples was detected by affinity

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Reprints not available.

Table 1.—Clinical Features of the Study Population

Clinical Group	Total No. (Female)	Mean ± SD Age, y	Mean ± SD Disease Duration, y
Clinically active multiple sclerosis			
Relapsing remitting	34 (20)	33.2 ± 5.7	7.9 ± 4.2
Chronic progressive	14 (9)	37.1 ± 7.6	9.4 ± 5.1
Clinically stable multiple sclerosis	16 (10)	35.6 ± 6.4	7.1 ± 5.6
Neurologic controls	32 (17)	40.2 ± 11.3	. . .
Normal subjects	18 (10)	31.5 ± 8.2	None
Total	**114 (66)**	35.5 ± 7.8	. . .

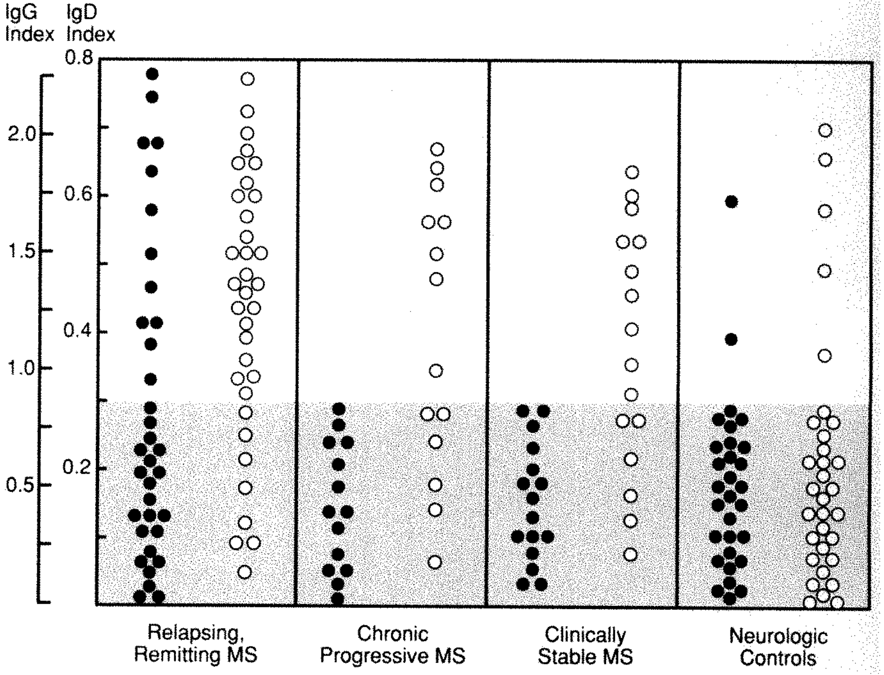

Fig 1.—Individual levels of IgD (closed circles) and IgG (open circles) indexes in the various study groups of patients with multiple sclerosis (MS). Shaded area represents the cutoff value of both indexes in the normal reference population. Statistical analyses are presented in the text.

purified rabbit peroxidase-conjugated antihuman δ chain (A-6281, Sigma). Known amounts of human IgD standard (OTRD 03, Behring, Marburg, Germany), as well as control CSF and serum, and background control wells were included in each plate. Optical densities of test samples were averaged, read from the standard curve, and corrected by the original dilution factor. Albumin and IgG concentrations in CSF and serum specimens were assayed by electroimmunoassay.[10] Total protein content in CSF was measured turbidometrically with the benzethonium chloride precipitation technique.[11]

Other CSF Tests

The CSF specimens were examined for pleocytosis within 6 hours of the lumbar puncture. Cell count was performed with the use of Fuchs-Rosenthal chambers (Hemocytometer, Aimer Products, London, England), and cytologic examination was performed with a Giemsa stain from a cytocentrifuge (Cytospin 2, Shandon Products Ltd, Cheshire, England) preparation. Oligoclonal κ and λ light chain bands in the CSF were detected by replicate immunoblotting technique.[12]

Evaluation of Intrathecal Immunoglobulin Synthesis

Intrathecal production of immunoglobulins was determined by calculating the immunoglobulin index value,[13] which compensates for the influence of leakage of immunoglobulin from the plasma into CSF. The immunoglobulin index was determined according to the following formula: CSF immunoglobulin × serum albumin/serum immunoglobulin × CSF albumin.

Magnetic Resonance Imaging (MRI)

All patients with clinically active MS underwent MRI as part of their routine investigations, and the images were reviewed by experienced radiologists who were "blinded" to the CSF data. Magnetic resonance imaging was performed on a 0.27-T superconducting imager (Picker International, Cleveland, Ohio). The same spin-echo sequence ($SE_{2000/60}$ [numbers are milliseconds]) was performed in all patients who underwent MRI.

Statistical Methods

Values were evaluated, as appropriate, by Spearman's Rank Correlation Coefficient, linear correlation coefficient, Student's t test, and the Wilcoxon Rank-Sum Test. Statistical analyses were performed with SPSS/PC$^+$ software (SPSS Inc, Chicago, Ill).

RESULTS

CSF IgD Estimation

The IgD enzyme-linked immunosorbent assay showed a coefficient of variation of 5.1% within and 5.8% between batches and had a detection limit of 0.2 ng/L. Separate studies on samples without aprotinin showed that addition of the protease inhibitor has improved detectability of CSF and serum IgD by a factor of 5. Detectability of IgG, however, was not altered by the addition of aprotinin.

One normal control subject was a high outlier for CSF IgD concentration, and the IgD amount was undetectable in three of the 18 normal control subjects and in two patients of the 32 subjects in the neurologic control group (one with Alzheimer's disease and another with epilepsy). These patients were excluded from the calculations of CSF IgD results.

In the reference control group, the CSF IgD showed a log normal distribution. Logarithmic transformation resulted in a mean ± SD reference CSF IgD of 1.86 ± 0.62 mg/L (range, 0.7 to 459 mg/L) and serum IgD of 1.54 ± 0.78 mg/L (range, 0.1 to 128 mg/L). The IgD index in the reference group was 0.12 ± 0.085, while the mean IgG index was 0.53 ± 0.16.

IgD Index in MS

High levels of IgD index were detected in the CSF of 12 patients (30%) with clinically active MS but was not detected in any patient with stable MS ($P<.01$; Fig 1). None of the patients with chronic progressive MS demonstrated a high IgD index value. Significantly higher IgD index values were seen in patients with active relapsing, remitting MS compared with the neurologic control group ($P<.02$). Only two neurologic control patients (6%) showed an abnormally high IgD index; one was suffering from type 1 hereditary sensory and motor neuropathy, while the other sustained a pontine infarct. Both also demonstrated high IgG index levels.

In patients with relapsing, remitting

MS, high IgD index levels correlated with the interval that separates the onset of a clinical relapse and the lumbar puncture. Of 21 patients who had the lumbar puncture within 1 week of a relapse, 11 (52%) demonstrated high IgD index values, while only one of 13 patients from whom CSF was collected more than a week (mean, 3.6 weeks) after the onset of relapse had a high IgD index ($P<.01$). High IgD index values, however, did not significantly correlate with the number of relapses in patients with relapsing, remitting disease. A negative correlation was found between IgD index and the total disease duration in patients with active MS (Fig 2).

IgD Index and CSF Features in MS

The relationship between IgD and IgG indexes in different groups of patients with MS has already been shown in Fig 1. Abnormally high IgD index levels were detected in two patients with active MS who had a normal IgG index. IgD index values in patients with MS failed to correlate with IgG index values ($r=.426$, $P=.08$). Furthermore, high IgG index values were detected in both clinically active and stable MS groups. Five patients (16%) in the neurologic control group had abnormally high IgG index levels: two presented with stroke, one with cervical spondylosis, and two with a high IgD index (see above).

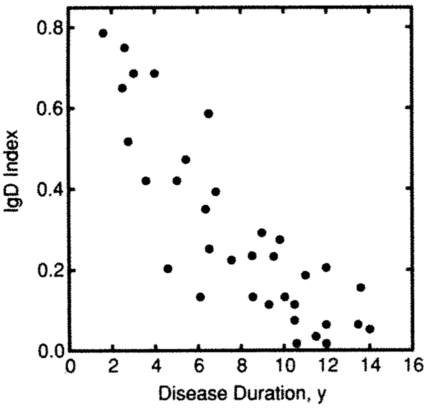

Fig 2.—Correlation of IgD index to total disease duration in patients with clinically active relapsing, remitting multiple sclerosis ($r=.857$, $P<.001$).

IgD index significantly correlated with CSF pleocytosis ($P<.005$) and with the detection of CSF reactive lymphocytes, ie, cells with altered staining characteristics due to increased cytoplasmic contents of immunoglobulins ($P<.01$; Table 2). A significant correlation was also found between high IgD index and the presence of free κ ($P<.005$) and free λ ($P<.001$) light chain bands in the CSF (Table 2). There was no significant correlation between IgD index and CSF-bound κ or λ light chain bands. Similarly, there was no correlation with CSF total protein content.

IgD Index and MRI Findings in MS

Table 3 summarizes data obtained from a comparison of MRI findings with IgD index values. High IgD index levels were detected in two patients with MS who had normal MRI scans. These two patients also had normal IgG index levels. No significant correlation was found between IgD index and either the total number of MRI lesions or their anatomic distribution.

COMMENT

Human IgD is different from other immunoglobulins in structure, exon arrangement, and physiologic location (reviewed by Blattner and Tucker[14]). The secreted form is a monomer, with a sedimentation rate of 7 *s*, which consists of two heavy (κ) and two light chains. Unlike other immunoglobulins, IgD has a relatively large hinge region that is sometimes present between the first and second region domains, probably to introduce flexibility into the structure to allow the antigen binding site to achieve better contact with antigens.[15] The suggestion that IgD has no function or that it simply serves as an auxiliary antigen receptor on B cells[16] seems a trivial interpretation of the evolution of such a complex system.[14] Despite its discovery two decades ago,[17] the biologic function(s) of soluble IgD is not fully understood because of its very low serum concentration. The levels of soluble IgD in human CSF are even lower, so when relatively insensitive methods of detection are utilized, none could be detected.[18,19] Furthermore, secreted IgD is susceptible to rapid proteolysis, probably by plasmine, although the addition of ε-aminocaproic acid, which is a relatively specific inhibitor of plasmine activation, failed to stop spontaneous protein degradation in some cases.[20] We found that the addition of enzyme inhibitor of a wider spectrum, eg, aprotinin, prevents protein fragmentation in all patients studied so far.

Results obtained in our reference group showed CSF and plasma levels of IgD and IgD index values relatively similar to those previously reported.[6,7] The data reported herein extend these reports and provide good evidence that intrathecal synthesis of IgD could be detected in a substantial number of patients with clinically active MS. The significant correlation of intrathecally synthesized IgD with clinical and

Table 2.—Correlation Between IgD Index and Other Cerebrospinal Fluid Features in Patients With Clinically Active Multiple Sclerosis, Including Those With Chronic Progressive Disease

	White Blood Cell Count, $\times 10^9$/L			κ Light Chain Bands		λ Light Chain Bands		Total Protein, g/L	
IgD Index*	<0.005	≥0.005	Reactive Lymphocytes	Free	Bound	Free	Bound	≤0.4	>0.4
High	1	11	8	7	5	11	7	5	7
Normal	28	8	1	0	4	3	6	22	14

*Normal index value is below 0.3.

Table 3.—Correlation of Intrathecal IgD Synthesis to Magnetic Resonance Imaging (MRI) Lesions (Locations of MRI Lesions Overlap) in Patients With Clinically Active Multiple Sclerosis, Including Those With Chronic Progressive Disease

		Location of MRI Lesions					
IgD Index Value (No. of Patients)	No. of MRI-Positive Patients	Periventricular	Cerebral	Cerebellar	Brain Stem	Cord	Mean No. of MRI Lesions
High (12)	10	8	7	7	3	2	21.9
Normal (36)	31	26	17	9	8	3	16.7
Total (48)	**41**	**34**	**24**	**16**	**11**	**5**	19.3

paraclinical variables in MS suggests that secreted IgD is not merely the result of cell surface shedding, as previously suggested.[21] Although systematic studies are warranted to establish the IgD profile in relation to clinical variables in greater detail, the detection of high IgD index values might have a place in routine characterization of the humoral immune response in patients with MS. Moreover, the demonstration that high IgD index values are predominantly detected in MS relapse may imply that they could be regarded as a reasonable indicator of relatively active disease. In contrast, no significant difference in intrathecal IgG synthesis was detected between clinically active and stable disease processes.

The absence of intrathecal synthesis of IgD in patients with chronic progressive MS is interesting. There have been several reports suggesting basic differences between chronic progressive and relapsing, remitting MS, which were based on genetic[22] and epidemiologic[23] studies. Furthermore, fundamental differences in clinical[23,24] and neuroimaging[25] features were noticed between the two MS groups. The data described in our study show a basic difference in the intrathecal IgD pattern between the two groups of patients with MS. In contrast, previous studies of CSF IgG, IgM, and IgA changes failed to detect any change in immunoglobulin pattern. Lolli and collaborators,[7] however, reported lower plasma IgD levels in patients with chronic progressive MS compared with those with relapsing, remitting disease.

The absence of a significant correlation between intrathecal IgD synthesis and MRI-detected lesion burden is not surprising. Muller and collaborators[26] failed to establish any correlation between CSF absolute γ-globulin production and quantified MRI changes in patients with MS. It is quite difficult to test for the relative number of new plaques in routine MRI, as chronic lesions are also visible.[27] Until the correlation between the measured factors in acute states is standardized, one should not draw conclusions as to the precise relationship among new plaques, intrathecal IgD synthesis, and the number of MRI-detected high signals.

The intrathecal production of IgD in 30% of patients with MS and the fact that this IgD production is mainly detected in patients with recent relapse indicates that IgD may play a role in the regulation of intrathecal humoral immune response in patients with MS.

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References

1. Goding JW, Scott DW, Layton JE. Genetics, cellular expression and function of IgD and IgM receptors. *Immunol Rev.* 1977;37:152-186.

2. Olson JC, Leslie GA. IgD: a component of the secretory immune system? In: Thorbecke GJ, Leslie GA, eds. *Immunoglobulin D: Structure and Function. Vol 399: Annals of the New York Academy of Science.* New York, NY: NY Academy of Sciences; 1982:98-104.

3. Patrick BA, Metha PD, Sobczyk W, et al. Measles virus-specific immunoglobulin D antibody in cerebrospinal fluid and serum from patients with subacute sclerosing panencephalitis and multiple sclerosis. *J Neuroimmunol.* 1990;26:69-74.

4. Neremberg ST, Prasad R. Radioimmunoassay for Ig classes G, A, M, D, and E in spinal fluid: normal values of different age groups. *J Lab Clin Med.* 1975;86:887-898.

5. Neremberg ST, Prasad R, Rothman MC. Cerebrospinal fluid IgG, IgA, IgM, IgD and IgE levels in central nervous system disorders. *Neurology.* 1978;28:988-990.

6. Out TA, Hische EA, van Walbeek HK, et al. Immunoglobulin D in cerebrospinal fluid. *Clin Chim Acta.* 1987;165:289-293.

7. Lolli F, Halawa I, Link H. Intrathecal synthesis of IgG, IgA, IgM, and IgD in untreated multiple sclerosis and controls. *Acta Neurol Scand.* 1989;80:238-247.

8. McDonald WI, Halliday AM. Diagnosis and classification of multiple sclerosis. *Br Med Bull.* 1977;33:4-8.

9. Fog T, Linnemann F. The course of multiple sclerosis. *Acta Neurol Scand.* 1970;46(suppl 47):1-175.

10. Laurell C-B. Electroimmunoassay. *Scand J Clin Lab Invest.* 1972;29(suppl 124):21-23.

11. Luxton R, Patel P, Keir G, Thompson E. A micro-method for measuring cerebrospinal fluid total protein using benzethonium chloride in microtitre plate wells. *Clin Chem.* 1989;35:1731-1734.

12. Thompson EJ, Keir G. Improved detection of oligoclonal and Bence-Jones proteins by κ/λ immunoblotting. *Clin Chim Acta.* 1984;143:329-335.

13. Tibbling G, Link H, Ohman S. Principles of albumin and IgG analyses in neurological diseases: establishment of reference values. *Scand J Clin Lab Invest.* 1977;37:285-390.

14. Blattner FR, Tucker PW. The molecular biology of immunoglobulin D. *Nature.* 1984;307:417-422.

15. Poljak RJ. Correlations between three-dimensional structure and function of immunoglobulins. *Crit Rev Biochem.* 1978;5:45-84.

16. Pure' E, Vitetta ES. The murine B cell response to TNP-polyacrylamide beads: the relationship between the epitope density of the antigen and the requirement for T cell help and surface IgD. *J Immunol.* 1980;125:420-427.

17. Rowe DS, Fahey JL. A new class of human immunoglobulins, I: a unique myeloma protein. *J Exp Med.* 1965;121:171-184.

18. Rowe DS, Crabbe' PA, Turner MW. Immunoglobulin D in serum, body fluids and lymphoid tissues. *Clin Exp Immunol.* 1968;3:477-490.

19. Tavolato B, De Zanche L. The IgD in the cerebrospinal fluid. *Acta Neurol Scand.* 1968;44:384-386.

20. Spiegelberg HL. The structure and biology of human IgD. *Immunol Rev.* 1977;37:3-24.

21. Hammarstrom L, Smith CIE. Immunoglobulin isotype diversity and its functional significance. In: French MA, ed. *Immunoglobulins in Health and Disease.* Lancaster, Pa: MTP Press Ltd; 1986:31-53.

22. Olerup O, Fredrikson S, Olsson T, et al. HLA class II genes in chronic progressive and in relapsing/remitting multiple sclerosis. *Lancet.* 1987;2:327.

23. Larsen JP, Kvaale G, Riise T, et al. Multiple sclerosis: more than one disease? *Acta Neurol Scand.* 1985;72:125-150.

24. Confavreux C, Aimard C, Devic N. Course and progression of multiple sclerosis assessed by the computerised data processing of 349 patients. *Brain.* 1980;103:281-307.

25. Thompson AJ, Kermode AG, MacManus DG, et al. Pathogenesis of progressive multiple sclerosis. *Lancet.* 1989;1:1322-1323.

26. Muller FA, Hanny PE, Wichmann W, et al. Cerebrospinal fluid immunoglobulins and multiple sclerosis: correspondence with magnetic resonance imaging and visually evoked potential changes. *Arch Neurol.* 1989;46:367-371.

27. Koopmans RA, Li DKB, Oger JJF, et al. The lesion of multiple sclerosis: imaging of acute and chronic stages. *Neurology.* 1989;39:959-963.

Serologic Evidence of *Campylobacter jejuni/coli* Enteritis in Patients with Guillain-Barré Syndrome

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• We performed serologic testing for *Campylobacter jejuni* in 17 consecutive patients with acute Guillain-Barré syndrome from the Boston, Mass area to compare the frequency of this preceding infection with the high rates reported from other areas of the world. The rate of seropositivity, 18%, was considerable, but it was lower than that reported in Australia. Moreover, all of our patients with definite serologic evidence of infection had severe enteritis before Guillain-Barré syndrome, usually with the organism cultured from stool samples. *Campylobacter* enteritis is an important antecedent illness for Guillain-Barré syndrome but did not precipitate the disease without enteritis.

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Acute infectious illnesses occur 1 to 3 weeks before Guillain-Barré syndrome (GBS) in approximately two thirds of patients, but specific pathogens are infrequently identified.[1,2] Infection with *Campylobacter jejuni/coli* has been highlighted as preceding GBS by a number of groups who have isolated the organism from the stool of patients with GBS or demonstrated *C jejuni/coli*–specific antibodies in serum or spinal fluid.[1-8] With the use of an enzyme-linked immunosorbent assay, Kaldor and Speed[2] found that 21 (38%) of 56 Australian patients with GBS had serologic evidence of *C jejuni* infection, and with the use of an immunodot assay, Speed et al[7] found *C jejuni/coli*–specific antibodies in 22 (49%) of 45 patients with GBS. These studies, if true in other geographic areas, would make *C jejuni* the most common pathogen that precedes GBS, exceeding the combined incidence of Epstein-Barr virus, cytomegalovirus, and *Mycoplasma* infections. *Campylobacter jejuni* is also interesting because it is one of the few bacteria that has been associated with GBS, and serologic evidence of infection in patients with GBS has been found in the absence of gastrointestinal symptoms.[2]

We therefore studied the frequency of *C jejuni/coli*–specific IgG, IgM, and IgA antibodies in 24 plasma and serum samples from 17 consecutive patients with GBS from the Boston, Mass area. Our results were similar to findings in a study from the United Kingdom,[8] but lower than the rates suggested by Australian studies. Moreover, all of our patients with definite serologic evidence of infection had severe enteritis.

PATIENTS AND METHODS

Patients

Seventeen consecutive patients who were admitted to the Massachusetts General Hospital, Boston, between January 1988 and January 1989, and who fulfilled the criteria for GBS according to the National Institute for Neurological and Communicative Disorders and Stroke, were studied (Table). All of the patients had typical acute GBS, although one subsequently had a course that was more consistent with relapsing inflammatory demyelinating neuropathy (Table, patient 5), one had severe GBS and prominent dysautonomia (Table, patient 16), and one later became ill with Hodgkin's disease (Table, patient 11).

Prodromal Illness

Six patients had preceding gastrointestinal illnesses, and six patients had respiratory prodromal illnesses, 1 to 47 days before neurologic symptoms, whereas five patients reported no illness (Table). Three of the patients with gastrointestinal prodromes had abdominal cramping, diarrhea (bloody in two patients), and fever that were compatible with bacterial enteritis. One patient was hospitalized for these symptoms and had no enteric pathogens cultured from a stool sample that was taken 47 days after the illness (Table, patient 7). Two other patients had *C jejuni* cultured from stool samples during the acute illness. Three patients had nausea, vomiting, or minimal nonbloody diarrhea. One of these patients had stool cultures, but no enteric pathogens were recovered. Of the six patients with respiratory illnesses, one had pneumonia with dry coughing and chills, as well as elevated titers of cold agglutinins, and another patient had fever, chills, and muscle aches that were thought to represent influenza; the remainder were described by patients as "colds."

Immunodot (Enzyme-Linked Immunosorbent Assay) of Plasma and Serum Samples

Fifteen serum samples were obtained from the 12 patients with a prodromal illness, 6 to 64 days (mean, 20 days) after the onset of the prodrome and 3 to 60 days (mean, 12 days) after the onset of GBS (Table). Nine samples were obtained from the five patients without a prodromal illness, 1 to 16 days (mean, 7 days) after the onset of GBS. Samples were stored at −20°C until serologic determinations were performed. Serum or plasma samples that were obtained from patients 6 to 15 days after the onset of gastroenteritis were considered to be positive if at least two of the three immunoglobulin classes demonstrated a titer of 400 or greater; serum

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Campylobacter jejuni/coli-Specific Antibody Titers From Consecutive Patients With GBS*

Patient	Preceding Illness	Stool Culture	Time, d: Prodrome Before GBS	Time, d: Serum After GBS	Antibody Titer: IgG	Antibody Titer: IgM	Antibody Titer: IgA
Group 1 (Definite Serologic Evidence of Infection)							
1	GI (enteritis)	Negative	47	4	800	233	533
2	GI (enteritis)	Positive	9	21	533	2133	467
3	GI (enteritis)	Positive	3	3	3200	800	3200
			...	8	2133	400	2133
Group 2 (Minor Elevation of Titers—No Evidence of Recent Infection)							
4	URI	...	20	3	400	267	<100
5	GI (mild)	Negative	4	10	<100	400	<100
6	URI	...	1	8	<100	267	<100
7	None	...	...	3	267	200	467
			...	10	<100	133	200
Group 3 (Low Titers)							
8	URI	...	0	8	<100	100	<100
9	GI	...	12	5	<100	<100	<100
10	Pneumonia	...	14	3	<100	<100	<100
11	None	...	...	1	<100	<100	<100
12	None	...	...	3	<100	<100	<100
13	None	...	...	5	<100	<100	<100
			...	12	<100	<100	100
14	None	...	...	8	<100	<100	<100
			...	16	<100	<100	<100
15	Influenza	...	0	9	<100	<100	<100
			...	14	<100	<100	<100
16	URI	...	7	9	<100	<100	<100
			...	11	<100	<100	<100

*GBS indicates Guillain-Barré syndrome; GI, gastrointestinal illness; and URI, upper respiratory tract illness. Day of onset of GBS was considered to be day "0."

or plasma samples that were obtained 16 to 64 days after the onset of gastroenteritis were considered to be positive if at least the IgG titers were 400 or greater.[9,10]

Immunodot assays of *C jejuni/coli*–specific IgG, IgM, and IgA antibodies were carried out by using the methods of Lior and Lacroix.[11]

Preparation of *C jejuni* Antigen Extracts

Antigen extracts of *C jejuni* serotype Lior 2 and *C coli* serotype Lior 12, found to give maximum heterologous reactivity with reference antiserum samples used for the serotyping of *Campylobacter*,[11] were prepared by the method described by McCoy et al.[12] Protein concentrations of the extracts were determined by the method of Lowry and colleagues.[13] Volumes of the two extracts that contained equal quantities of protein were pooled and lyophilized.

Determination of Properties of *C jejuni*

Serotyping of *C jejuni* was carried out by the method of Lior et al,[14] bacteriophage typing was done by the method of Grajewski et al,[15] biotyping was performed by the method of Lior,[16] and cytotoxic and cytotonic analyses were done according to the method described by Johnson and Lior.[17]

RESULTS

Three patients (Table, group 1) had serologic evidence of *Campylobacter* enteritis, with two of three antibody titers above 400. Samples from these three patients were obtained 51, 30, and 6 days after the onset of diarrhea and 47, 21, and 3 days after neurologic symptoms began. A second sample in patient 3 (Table), taken 5 days after the first, demonstrated slightly lower, but still elevated titers in all immunoglobulin classes. Each of the three patients with serologic evidence of infection had a severe gastrointestinal illness with diarrhea, and two (Table, patients 2 and 3) had *C jejuni* isolated from stool samples. The organism that was isolated from the stool of patient 3 (Table) was found to belong to serogroup 1, biotype I, and phage type 36; cytotoxic and cytotonic assays were negative.

Group 2 patients had some antibody titer elevation above 200, not high enough to make a serologic diagnosis of *Campylobacter* infection. Although the serum of patient 4 (Table) demonstrated an IgG titer of 400, this patient was not considered to have been infected with *C jejuni* because the other titers were low, and the prodromal illness was not gastroenteritis. Patient 5 (Table) did have mild gastrointestinal symptoms, but the plasma sample was obtained 14 days afterward, when the *C jejuni* serologic response usually peaks.[9,10] Instead, the IgM titer was only 400, with IgA and IgG titers below 100.

COMMENT

In this study, three of 17 consecutive patients with GBS had both clinical and serologic evidence of *C jejuni* infection and *C jejuni* was recovered from the stools of two patients. Failure to isolate *C jejuni* from a third patient was not surprising as the stool was obtained 47 days after enteritis.[18] The relatively low IgM and IgA titers in plasma samples that were obtained 51 days after diarrhea in this patient were consistent with data that showed that these titers decline, beginning 2½ to 4 weeks after infection, whereas IgG titers persist for longer.[9,10] Our group with only one class of titer above 400 was unlikely to have had recent *Campylobacter* infection.

The correlation among severe enteritis, positive *C jejuni*–specific serology, and the presence of *C jejuni* in stool in US patients is similar to the findings of Winer et al[8] in a study from the United Kingdom, but differs from the findings of two Australian studies.[2,7] The Australian series included larger groups of patients with GBS, of whom a high proportion (38% and 49%) were considered to have been infected with *C jejuni* on the basis of serologic findings alone.[2,7] Patients with and without gastroenteritis had serologic evidence of infection, but the organism was isolated from only two of 43 patients. The inclusion of our second group of patients with marginally elevated titers would make the proportion of *Campylobacter* that precedes GBS similar to some previous studies. The differences between our results and those of previous studies may also reflect different serologic techniques or differences between populations that live in different parts of the world. The series compiled by Winer et al[8] in the United Kingdom is similar to ours, with 14% of patients having had serologic evidence of *C jejuni*. However, the consistent finding of even a low incidence of *C jejuni*–infected patients with GBS reinforces the evidence that *C jejuni*, the only bacterial pathogen that regularly precedes GBS, has an incidence comparable with Epstein-Barr virus, cytomegalovirus, or *Mycoplasma* infection.[19,20] The incidence of prior *C jejuni* infection is probably lower than that reflected in our consecutive series, since six (35%) of 17 patients had a gastrointestinal prodrome. In contrast, only 10% of a larger prospective series,[21] and 17% in the United Kingdom series,[8] had a diarrheal illness. Additional studies on consecutive series of patients may allow a better approximation of the frequency and population variations of GBS preceded by *C jejuni* infection.

The recent finding of cross-reactivity between antigens from *C jejuni* and the P2 protein of peripheral nerve myelin may explain the pathogenetic connection between the infection and GBS[22] and possibly some of the marginally elevated titers in our second group of patients.

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References

1. Sovilla JY, Regli F, Francioli PB. Guillain-Barré syndrome following *Campylobacter jejuni* enteritis. *Arch Intern Med.* 1988;148:739-741.
2. Kaldor J, Speed BR. Guillain-Barré syndrome and *Campylobacter jejuni:* a serological study. *BMJ.* 1984;288:1867-1870.
3. Rhodes KM, Tattersfield AE. Guillain-Barré syndrome associated with *Campylobacter* infection. *BMJ.* 1982;285:173-174.
4. Molnar GK, Mertsola J, Erkko M. Guillain-Barré syndrome associated with *Campylobacter* infection. *BMJ.* 1982;285:652.
5. Pryor WM, Freiman JS, Gillies MA, Tuck RR. Guillain-Barré syndrome associated with *Campylobacter* infection. *Aust N Z J Med.* 1984;14:687-688.
6. Ropper AH. *Campylobacter* diarrhea and Guillain-Barré syndrome. *Arch Neurol.* 1988;45:655-656.
7. Speed BR, Kaldor J, Watson J, et al. *Campylobacter jejuni/Campylobacter coli*–associated Guillain-Barré syndrome: Immunoblot confirmation of the serological response. *Med J Aust.* 1987;147:13-16.
8. Winer JB, Hughes RAC, Anderson MJ, Jones DM, Kangro H, Watkins RPF. A prospective study of acute idiopathic neuropathy, II: antecedent events. *J Neurol Neurosurg Psychiatry.* 1988;51:613-618.
9. Blaser MJ, Duncan DJ. Human serum antibody response to *Campylobacter jejuni* infection as measured in an enzyme-linked immunosorbent assay. *Infect Immun.* 1984;44:292-298.
10. Kaldor J, Pritchard H, Serpell A, Metcalf W. Serum antibodies in *Campylobacter* enteritis. *J Clin Microbiol.* 1983;18:1-4.
11. Lior H, Lacroix R. Detection of *Campylobacter jejuni* and *Campylobacter coli* serum antibodies using a paper enzyme-linked immunosorbent assay. In: Pearson AD, Skirrow MB, Rowe B, Davies JR, Jones DM, eds. Campylobacter *II: Proceedings of the Second International Workshop on* Campylobacter *Infections, Brussels, Belgium.* London, England: Public Health Laboratory Service; 1983:72-73.
12. McCoy EC, Doyle D, Burda K, Corbeil LB, Winter AJ. Superficial antigen of *Campylobacter* (*Vibrio*) fetus: characterization of an antiphagocytic component. *Infect Immunol.* 1975;11:517-525.
13. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ. Protein measurement with the folin phenol reagent. *J Biol Chem.* 1951;193:265-275.
14. Lior H, Woodward DL, Edgar JA, LaRoche LJ, Gill P. Serotyping of *Campylobacter jejuni* by slide agglutination based on heat-labile antigenic factors. *J Clin Microbiol.* 1982;15:761-768.
15. Grajewski BA, Kusek JW, Gelfand HM. Development of a bacteriophage typing system for *Campylobacter jejuni* and *Campylobacter coli. J Clin Microbiol.* 1985;22:13-18.
16. Lior H. New, extended biotyping scheme for *Campylobacter jejuni, Campylobacter coli,* and *Campylobacter laridis. J Clin Microbiol.* 1984;20:636-640.
17. Johnson WM, Lior H. Cytotoxic and cytotonic factors produced by *Campylobacter jejuni, Campylobacter coli,* and *Campylobacter laridis. J Clin Microbiol.* 1986;24:275-281.
18. Blaser MJ. *Campylobacter* infections. In: Evans AS, Feldman HA, eds. *Bacterial Infections of Humans: Epidemiology and Control.* New York, NY: Plenum Medical Book Co; 1982:145.
19. Grose C, Henle W, Henle G, Feorino PM. Primary Epstein-Barr virus infections in acute neurologic diseases. *N Engl J Med.* 1975;292:392-395.
20. Goldschmidt B, Menonna J, Fortunato J, Dowling P, Cook S. *Mycoplasma* antibody in Guillain-Barré syndrome and other neurological disorders. *Ann Neurol.* 1980;7:108-112.
21. Ropper AH, Wijdick EFM, Truax BT. *Guillain-Barré Syndrome.* Philadelphia, Pa: FA Davis Co Publishers; 1991.
22. Fujimoto S, Amako K. Guillain-Barré syndrome and *Campylobacter jejuni* infection. *Lancet.* 1990;335:1350.

Autonomic Nervous Function in Progressive Supranuclear Palsy

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• Autonomic nervous function was assessed in 11 patients with progressive supranuclear palsy, 26 patients with Parkinson's disease, matched for age, medications, disease severity, and disease duration, and 19 age-matched controls. Results of both parasympathetic (heart rate response to deep breathing and Valsalva maneuver) and sympathetic (blood pressure decrease on standing and increase on sustained handgrip) tests were abnormal in both patient groups. Abnormalities in the group of patients with progressive supranuclear palsy were similar to those in the group with Parkinson's disease but were more pronounced. Autonomic dysfunction may have to be considered a feature of progressive supranuclear palsy.

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Autonomic dysfunction has not been considered a clinical feature of progressive supranuclear palsy (PSP).[1-3] The distribution of neuropathologic involvement in PSP reveals that several structures related to autonomic function are affected, such as the hypothalamus and the locus coeruleus.[1-4] We compared autonomic function in patients with PSP with that in healthy age-matched controls and patients with idiopathic Parkinson's disease (PD).

PATIENTS AND METHODS

Informed consent was obtained from all subjects, and approval was obtained from the local medical ethics committee. Diseases or medications affecting the autonomic nervous system were exclusion criteria.

Eleven patients with PSP were enrolled in the study (mean [SD] age, 75.5 [6.4] years; mean [SD] duration of motor symptoms, 3.5 [2.1] years; six patients were male). The diagnosis was based on established criteria[3]: a late-onset progressive nonfamilial disorder with supranuclear ophthalmoplegia and at least two of the following features: axial dystonia or rigidity, pseudobulbar palsy, bradykinesia, frontal lobe signs, and postural instability. As there is no specific disability scale for PSP, we used the Hoehn and Yahr[5] scale to express disease severity; six patients had stage III disease, and five had stage IV disease. Seven patients were being treated with levodopa, two with amantadine hydrochloride, and one with bromocriptine mesylate, alone or in combinations; four were taking no medication.

The patients were compared with 19 healthy age-matched controls (mean [SD] age, 74.3 [8.3] years; four subjects were male) and with 26 patients with PD (mean [SD] age, 73.5 [6.7] years; mean [SD] duration, 4.1 [4.0] years; 12 patients were male). Twelve patients with PD were taking levodopa, six were taking amantadine, and three were taking bromocriptine, alone or in combination; 12 were taking no medication. Two patients with PD had Hoehn and Yahr[5] stage II disease, 16 had stage III disease, seven had stage IV disease, and one had stage V disease.

Autonomic tests are influenced by age and possibly by antiparkinsonian drugs; some tests require physical and mental cooperation. Age, medications, and disease duration and severity were thus used as selection criteria for the PD group. Age and disease duration did not differ (Student's t test, $P=.5$) between the groups. The use of medication, as mentioned above, did not differ between the PSP and PD groups (χ^2 test, $P>.05$). The proportions of patients in Hoehn and Yahr disease stages did not differ (χ^2 test, $P=.59$).

The six autonomic function tests used have been previously described.[6] Heart rate variation was measured at rest, during forced breathing, on standing, and during a Valsalva maneuver. Maximum and minimum frequencies, derived from individual beat intervals, were used to calculate differences and ratios. Systolic and diastolic blood pressures were measured while the subjects were lying down and 1 and 2 minutes after they stood up. The pressure decrease was defined as the difference between starting and minimum pressures at 1 or 2 minutes. In the sustained handgrip test, blood pressure was measured every minute before and for 5 minutes after or until the subject gave up after the start of contraction. The difference between maximum and starting pressures defined the pressure increase.

Differences were investigated with analysis of variance and Student's t test. A significance threshold of $P<.05$ was used; values of $.05<P<.10$ were considered trends toward significance.

RESULTS

A consistent order of increasing abnormality (control, PD, PSP) was found for four of the six tests (Table, Figs 1 and 2). Statistically significant differences (by analysis of variance) were found for heart rate variation in the standing test and for blood pressure increase in the sustained handgrip test. When only the PSP and control groups were compared, the blood pressure response to standing also differed significantly.

COMMENT

We found evidence of sympathetic (blood pressure tests) and parasympathetic (heart rate tests) disturbances in patients with PSP compared with controls. Although not all comparisons resulted in significant differences, the consistent ranking of results in the order control, PD, and PSP suggests that this is explained by the limited number of patients or the large variability of test results (Valsalva maneuver and blood pressure to standing tests).

The autonomic dysfunction in the PD group is in line with earlier reports.[7-11] The pattern of abnormalities is similar in PSP and PD, suggesting that the same structures are damaged in PSP as

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Results of Autonomic Function Tests in 11 Patients With Progressive Supranuclear Palsy (PSP), 26 With Parkinson's Disease (PD), and 19 Healthy Controls (C)*

	C	PD	PSP	ANOVA	C-PD	C-PSP	PD-PSP
Heart rate, beats per minute	82.1 (14.8)	75.9 (14.2)	77.8 (20.7)	–	. . .	. . .	. . .
Systolic BP, mm Hg	139.7 (15.9)	136.7 (17.8)	131.7 (18.7)	–	. . .	. . .	. . .
Diastolic BP, mm Hg	81.1 (6.9)	80.7 (10.7)	79.4 (9.8)	–	. . .	. . .	. . .
Heart rates							
Ratios							
Rest	1.15 (0.01)	1.16 (0.11)	1.13 (0.07)	–	. . .	. . .	. . .
Breathing	1.21 (0.22)	1.20 (0.15)	1.21 (0.15)	–	. . .	. . .	. . .
Standing	1.18 (0.16)	1.10 (0.10)	1.08 (0.09)	*	T	*	–
Valsalva maneuver	1.31 (0.22)	1.26 (0.21)	1.18 (0.16)	–	. . .	. . .	. . .
Differences							
Rest	11.0 (6.2)	8.7 (4.1)	9.8 (4.7)	–	. . .	. . .	. . .
Breathing	14.9 (11.9)	10.9 (5.9)	11.3 (4.7)	–	. . .	. . .	. . .
Standing	12.2 (11.4)	6.4 (7.1)	0.0 (2.4)	*	T	**	**
Valsalva maneuver	21.3 (14.2)	18.1 (18.0)	13.9 (10.0)	–	. . .	. . .	. . .
BP							
Standing							
Systolic decrease	11.2 (10.9)	11.5 (18.2)	15.8 (11.7)	–	. . .	. . .	. . .
Diastolic decrease	1.4 (5.1)	5.5 (9.0)	7.0 (7.3)	–	(T	*	–)
Sustained handgrip							
Systolic increase	29.2 (24.9)	18.4 (15.8)	11.6 (8.1)	*	–	**	–
Diastolic increase	25.6 (22.3)	14.4 (15.6)	8.4 (8.3)	*	T	**	–

*Baseline heart rate is given as the mean rate of the resting test. Blood pressure (BP) values refer to baseline values in the standing test. Values are mean (SD). Significance levels are given for analysis of variance (ANOVA) and Student's *t* test; minus sign indicates $P > .10$; single asterisk, $P < .05$; double asterisk, $P < .01$; T, trend: $.05 < P < .10$.

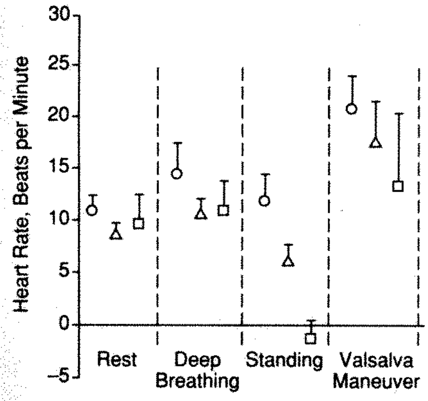

Fig 1.—Mean differences between maximum and minimum heart rates are illustrated for four heart rate tests and all three groups. Vertical bars indicate 1 SE; circles, control group; triangles, Parkinson's disease group; and squares, progressive supranuclear palsy group.

in PD, but more severely. Autonomic dysfunction in PD has been attributed to damage to the hypothalamus.[12,13] As damage to this structure also occurs in PSP,[14] this is a likely explanation for autonomic dysfunction in PSP as well.

Matching for medication makes it unlikely that the difference in severity was caused by medication. This is supported by studies in which no effect of antiparkinson treatment was found on autonomic function in PD.[7-9] An improvement of autonomic nervous function after levodopa treatment has in fact been documented.[11] Only dopamine agonist therapy appears to influence autonomic function,[10] but only one of our patients was taking this medication.

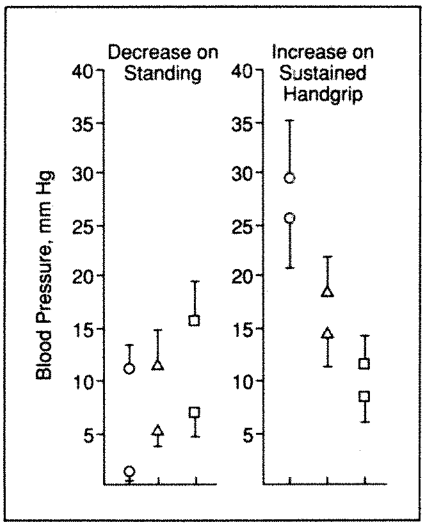

Fig 2.—Mean systolic and diastolic blood pressures are depicted for each of the three groups, for the standing and for the sustained handgrip tests. Vertical bars indicate 1 SE; circles, control group; triangles, Parkinson's disease group; and squares, progressive supranuclear palsy group.

The absence of dysautonomia has been proposed as a prerequisite for the diagnosis of PSP.[11] In view of our results, we suggest that dysautonomia may instead have to be included in the list of less constant and minor symptoms of PSP.

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References

1. Steele JC, Richardson JC, Olszewski J. Progressive supranuclear palsy. *Arch Neurol.* 1964;10:333-359.
2. Ostergaard Kristensen M. Progressive supranuclear palsy: 20 years later. *Acta Neurol Scand.* 1985;71:177-189.
3. Lees AJ. The Steele-Richardson-Olszewski syndrome (progressive supranuclear palsy). In: Marsden CD, ed. *Movement Disorders.* Stoneham, Mass: Butterworth; 1987:272-287.
4. Tanner CM, Goetz CG, Klawans HL. Autonomic nervous system disorders. In: Koller WC, ed. *Handbook of Parkinson's Disease.* New York, NY: Marcel Dekker Inc; 1987:145-170.
5. Hoehn HM, Yahr MD. Parkinsonism: onset, progression and mortality. *Neurology.* 1967;37:1173-1178.
6. den Heijer JC, Bollen ELEM, Reulen JPH, et al. Autonomic nervous function in Huntington's disease. *Arch Neurol.* 1988;45:309-312.
7. Appenzeller O, Goss JE. Autonomic deficits in Parkinson's syndrome. *Arch Neurol.* 1971;24:50-57.
8. Kuroiwa Y, Shimada Y, Toyokura Y. Postural hypotension and low R-R interval variability in parkinsonism, spino-cerebellar degeneration and Shy-Drager syndrome. *Neurology.* 1983;33:463-467.
9. Goetz CG, Lutge W, Tanner CM. Autonomic dysfunction in Parkinson's disease. *Neurology.* 1986;36:73-75.
10. Ludin SM, Steiger UH, Ludin HP. Autonomic disturbances and cardiovascular reflexes in idiopathic Parkinson's disease. *J Neurol.* 1987;235:10-15.
11. Camerlingo M, Ferraro B, Gazzaniga GC, Casto L, Cesana BM, Mamoli A. Cardiovascular reflexes in Parkinson's disease: long-term effects of levodopa treatment on de novo patients. *Acta Neurol Scand.* 1990;81:346-348.
12. Langston JW, Forno LS. The hypothalamus in Parkinson disease. *Ann Neurol.* 1978;3:129-133.
13. Javoy-Agid F, Ruberg M, Pique L, et al. Biochemistry of the hypothalamus in Parkinson's disease. *Neurology.* 1984;34:672-675.
14. Golbe LI, Davis PH, Schoenberg BS, Duvoisin RC. Prevalence and natural history of progressive supranuclear palsy. *Neurology.* 1988;38:1031-1034.

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Dr. Aliza Lifshitz, Internist, Los Angeles, California, Member, American Medical Association

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Acute Hemorrhagic Leukoencephalitis

A Successful Recovery

David Seales, MD, PhD, Melvin Greer, MD

• A 50-year-old woman developed acute hemorrhagic leukoencephalitis approximately 7 days after the onset of a benign respiratory infection. Mycoplasmal pneumonia was suspected because of Coomb's positive hemolysis, cold agglutinins, and sensitivity to erythromycin base but was not proved. Acute hemorrhagic leukoencephalitis was demonstrated by brain biopsy 24 hours after admission. The patient recovered without lasting sequelae following reduction of increased intracranial pressure by mannitol, hyperventilation, and phenobarbital and prolonged immunosuppression by plasmapheresis, steroids, and cyclophosphamide.

(*Arch Neurol.* 1991;48:1086-1088)

Acute hemorrhagic leukoencephalitis (AHL) was established as a pathologic entity in 1941.[1] This fulminant, myelinoclastic disease of the central nervous system is characterized by the development over hours to days of severe neurologic symptoms of confusion, dysarthria and/or aphasia, hemiparesis, seizures (focal or generalized), and, occasionally, acute myelitis. Fever, often remarkably high, may be present. Coma and death usually follow within a week. A prodromal illness (usually a viral upper respiratory infection) usually occurs days to 3 weeks before the onset of AHL, with apparent recovery.[2] Acute hemorrhagic leukoencephalitis was considered uniformly fatal, although survival has occurred in isolated cases treated with surgical decompression, corticosteroids, or plasma exchange.[3-5] The patient described herein was treated aggressively with plasmapheresis, corticosteroids, and cyclophosphamide and had intracranial pressure (ICP) monitoring. The patient recovered without residua.

REPORT OF A CASE

For 1 week, a previously healthy, right-handed, 50-year-old white woman had a cough and low-grade fever. Chest roentgenography revealed a diffuse interstitial infiltrate. The cough improved with oral erythromycin base therapy (500 mg every 6 hours). Seven days after the onset of her illness, the patient developed severe neck pain, occipital headache, and slurred speech. When discovered 8 hours later by her husband, she was lethargic and left-sided weakness was apparent.

In the emergency department 2 hours later, her blood pressure was 150/100 mm Hg; pulse rate, 92 beats per minute; respiration rate, 24 breaths per minute; and temperature, 37.8°C rectally. There was no nuchal rigidity. She picked aimlessly in the air. Intermittently, she would squeeze the examiner's hand in response to command; she squeezed with the right hand only. She opened her eyes to painful stimulation but did not speak. Her pupils were pinpoint (1.5 mm) but briskly reactive to light. Roving, conjugate, horizontal eye movements were present but alternated with a right gaze preference. Her mouth was held rigidly closed. She perceived pinprick diffusely as assessed by withdrawal and facial response. Strength (assessed during spontaneous movements) was reduced diffusely in the left hemibody (4/5 upper extremity; 4+/5 lower extremity). Tone was increased in the left upper extremity. Deep tendon reflexes were symmetrical and hyperactive diffusely. A Babinski's sign was present on the left.

A chest roentgenogram revealed a resolving left midlung field infiltrate. Computed tomography of the head before and after perfusion with contrast (Hypacque, 100 mL intravenous 60% solution) revealed a nonenhancing low-density area in the right frontal and parietal lobes, with a slight mass effect. Arterial blood gas analysis disclosed the following values: pH, 7.38; Pco$_2$, 44 mm Hg, Po$_2$, 45 mm Hg; bicarbonate, 25.3 mEq/L; and oxygen saturation, 77%. The white blood cell count was 23.2×10^9/L. The differential cell count was 0.76 polymorphonuclear leukocytes, 0.11 band cells, 0.06 lymphocytes, and 0.07 monocytes. Samples of the patient's blood held at bedside agglutinated at room temperature. Coomb's positive reactivity was noted with a cold agglutinin (titer 1:640). The agglutinin was not directed against the anti-I antigen on the red blood cell surface. Sedimentation rate (Westergren) was 25 mm/h.

Acyclovir sodium (loading dose, 1 g; maintenance dose, 700 mg every 8 hours), penicillin G potassium (2 million U every 4 hours), chloramphenicol sodium succinate (500 mg every 6 hours), and phenytoin sodium (loading dose, 500 mg; maintenance dose, 100 mg every 8 hours) were administered intravenously.

At 12 hours after admission, a nasal airway was placed because of increased upper airway obstruction with tracheal retraction. At 14 hours, there was coffee grounds emesis. At 15 hours, after experiencing difficulty with nasogastric tube placement, the patient was in respiratory distress (pH, 7.04; Pco$_2$, 71 mm Hg; Po$_2$, 30 mm Hg; bicarbonate, 19 mEq/L; and oxygen saturation, 34%. Endotracheal intubation was performed. Arterial blood gases returned to pH, 7.46; Pco$_2$, 28 mm Hg; Po$_2$, 158 mm Hg; and oxygen saturation, 99% (intermittent mandatory ventilation, 12 breaths per minute; positive end-expiratory pressure, 5 cm H$_2$O; and 50% oxygen).

Seventeen hours after admission, decerebrate posturing was evident in response to stimulation. The right pupil dilated (6 mm) and became nonreactive to light; the left pupil dilated to 3 mm and was sluggishly reactive to light. Ankle clonus and Babinski's signs were present bilaterally. Hyperventilation was begun. Mannitol (50 mg per intravenous dose), phenobarbital sodium (loading dose, 550 mg; maintenance dose, 250 mg/d), and dexamethasone sodium phosphate (Decadron, 6 mg per nasogastric tube every 6 hours) were administered.

Twenty-two hours after admission, erythromycin base (1 g administered intravenously every 6 hours) and ceftriaxone sodium (loading dose, 2 g; maintenance dose, 2 g administered intravenously every 24 hours) therapy was begun. Penicillin and chloramphenicol therapy was discontinued.

Brain biopsy was performed at the right frontal region 24 hours after admission. In white matter, there were microhemorrhages and focal acute fibrinoid necrosis of small vessels; the cortex was completely spared. Vacuolization, lymphocytes, polymorphonuclear leukocytes, and erythrocytes were present in perivascular white matter spaces. No inclusion bodies were seen, and stains for bacteria, acid-fast bacilli, India ink, *Toxoplasma*, herpes simplex, and fungi were negative. Acyclovir and ceftriaxone therapy was discontinued.

At the time of biopsy, an ICP monitor was inserted anterior to the site of the biopsy. The ICP remained elevated (16 to 19 mm Hg) for the second 24 hours of hospitalization. Thereafter, the ICP could be held between 10 and 15 mm Hg by the intravenous administration of mannitol (50 mg) when the ICP increased to 15 to 20 mm Hg. Arterial pH was maintained at 7.45 to 7.50 with the Pco$_2$ at 30 mm Hg.

The patient's neurologic status showed gradual improvement after 32 hours. Her

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pupils were 1.5 to 2.0 mm bilaterally; her left pupil showed minimal response to light. Her oculocephalic reflex and corneal reflexes were still depressed. She was still hyperreflexic but no longer had ankle clonus. At 35 hours, a sternal rub elicited extensor posture.

The hematocrit dropped from 0.35 at admission to 0.16 thirty-six hours after admission. The drop in hematocrit was thought to be secondary to hemolysis (corrected reticulocyte count, 2.1%; total bilirubin, 32.3 μmol/L; direct bilirubin, 3.4 μmol/L). Packed red blood cells (2 U) were given. Intravenous methylprednisolone sodium succinate (Solu-Medrol) therapy (60 mg every 6 hours) was initiated.

At 36 hours, plasmapheresis (3 L exchange with a solution of 1500 mL of 5% albumin per 1500 mL of normal saline) was begun daily for 5 days. Electroencephalography revealed diffuse slowing in the anterior hemisphere (more pronounced on the left than on the right) consistent with encephalopathy. By 49 hours, the patient's pupils were 3 mm and reactive to light with presence of the oculocephalic response and bilateral corneal reflexes. The pharyngeal reflex was intact. Extensor posturing was still noted in response to pain. By 96 hours, extensor tone occurred in the extremities at rest. By 110 hours, eye movements fluctuated from oculocephalic reflex only to spontaneous, conjugate, roving eye movements. Ventilatory assistance was still required; spontaneous respirations were present only when the patient was stimulated. She still demonstrated extensor tone at rest but withdrew all four extremities to painful stimulation. She opened her eyes to sternal rub. By days 6 and 7, the presence of corneal reflexes was variable. Plasmapheresis was concluded on hospital day 7. By day 8, her eyes were deviated downward (left eye more than right). Her pupils were small and unreactive. Tone alternated between flaccid and rigid.

On hospital day 8, cyclophosphamide therapy (180 mg/d) was begun. Erythromycin therapy was discontinued. By hospital day 9, spontaneous respirations had returned, and the patient underwent extubation. Her neurologic status gradually improved. Purposeful eye movements occurred in response to verbal inquiry. Spontaneous movements of the body and then meaningful speech returned. Left-sided weakness resolved to a large extent.

A lumbar puncture on day 28 revealed the following values: opening pressure, 220 mm of cerebrospinal fluid with no red or white blood cells; glucose, 4.1 mmol/L; and protein, 0.28 g/L. Cerebrospinal fluid stains (India ink, acid-fast bacilli, and bacterial) and cultures (tuberculin, fungal, bacterial, and viral) showed no growth. Serologic tests were negative for cerebrospinal fluid, VDRL, and cryptococcal antigens.

Thirty-two days after admission, the patient was discharged. Mild recent memory impairment was evident. There were no deficits in immediate or remote memory. Orientation, judgment, content, affect, speech, reading, writing, naming, comprehension, left-right orientation, finger naming, calculation, buccofacial and appendicular praxis, figure drawing, mapping, stereognosis, and graphesthesia were intact. There was no neglect or perseveration. There was vertical diplopia (most marked with gaze to the lower left visual field) and mild weakness in the left hip flexors. Tone was increased in the left lower extremity. Cyclophosphamide had been given intravenously for 23 days (180 mg/d on days 8 through 10 and 12 through 24, tapered over the next 7 hospital days. The patient had received methylprednisolone sodium succinate (60 mg every 6 hours) on days 3 through 10 and oral prednisone (60 mg/d) on days 13 through 17 with tapering over days 18 through 39.

Follow-up computed tomographic scans of the head on hospital days 15 and 39 revealed reduced edema without cystic degeneration in the right frontoparietal regions. Acute and convalescent titers of mycoplasmal pneumonia, herpes simplex, rubella, influenza A and B, Epstein-Barr virus, parainfluenza III, equine encephalomyelitis, St Louis encephalitis, cytomegalovirus, and legionnaire's disease were negative for current infection. Tests were negative for human immunodeficiency virus. Six months after the onset of her illness, the patient resumed her previous employment. Four years later, the findings of her examination remained normal.

COMMENT

Approximately 70 cases of AHL are documented in the English language literature.[6-8] Both sexes are affected equally, with an age range of 2.5 to 60 years.[3] The lack of reported cases before approximately 3 years of age may relate to the incomplete myelinization of cerebral white matter before this age. A temporal relationship has been noted between certain common illnesses, such as upper respiratory infections, varicella, and bronchial pneumonia, and the subsequent development of AHL in the following days or weeks.[5] Acute hemorrhagic leukoencephalitis has also been noted following or in association with processes as diverse as removal of tooth stumps, herniorrhaphy, injection of pertussis vaccine, herpes simplex, thrombotic thrombocytopenic purpura, and application of arsphenamine to the gums.[3,9]

The incidence of AHL complicating atypical pneumonia is probably less than 0.1%.[10] Coomb's positive hemolysis and cold agglutinins are seen, especially in relation to *Mycoplasma pneumoniae* infection.[11]

In the present case, infection with *M pneumoniae* was suspected, but acute and convalescent titers were negative. Furthermore, the cold agglutinins did not react with polysaccharide antigen expressed on the surface of adult erythrocytes as is noted in mycoplasmal pneumonia. No other viral titers were positive for current infection. Thus, the precise nature of the atypical pneumonia in the present case is unknown.

The differentiation of AHL from herpes simplex encephalitis can be difficult. Fever, headache, hallucinations, focality of neurologic abnormalities, and acuteness do not differentiate the two diseases. Examination of cerebrospinal fluid may exclude bacterial, fungal, and mycobacterial infection but will not differentiate AHL from herpes simplex. Thus, early brain biopsy is advocated. In AHL, necrotizing angiitis of venules and capillaries of white matter is noted microscopically. Gray matter and subcortical U-shaped fibers are usually spared as opposed to the gray and white matter damage observed in herpes simplex encephalitis. In AHL, ball-and-ring hemorrhages form around affected vessels, with fibrinoid necrosis and polymorphonuclear leukocytes evident in vessel walls. Later, lymphocytes replace the polymorphonuclear leukocytes; lipid phagocytosis is seen if survival is several days. Grossly, the lesions are usually unilateral in the parietal or posterior frontal regions, but may be bilaterally symmetrical. Lesions can occur in other regions as well, including the brain stem and spinal cord.[2,3]

The lesions of AHL can be demonstrated by computed tomography.[12] Furthermore, it has been proposed that with computed tomography one may be able to distinguish between AHL and herpes simplex encephalitis.[13] This is based on the findings that in AHL the computed tomographic findings arise earlier (in 1.5 days as opposed to 3 to 11 days for herpes simplex), are restricted to white matter, and do not enhance with contrast.

The pathogenesis of AHL is unknown. An immunoreactive basis is supported by (1) the latent period between preceding illness and onset of AHL, (2) the lack of identification of an infecting organism, (3) the relation to immunization, (4) the atopy observed in many patients with AHL, and (5) the similarity to a fulminant form of experimental allergic encephalitis.[2] In animals, experimental allergic encephalitis is a model of acute disseminated leukoencephalitis; it is also a white matter myelinoclastic process but of less acute course than AHL.[14] In addition, DNA-synthesizing lymphoblasts have been observed in the peripheral blood of a patient with AHL, as well as in animals with experimental allergic encephalitis.[15]

Success in the treatment of AHL has been modest. Two of five proved cases survived following surgical decompression.[16] High-dose steroids (10 mg of dexamethasone administered intravenously, then 6 mg every 6 hours) have been thought to aid in the survival of patients with AHL.[3,4] More recently, plasma exchange was used successfully in one patient with neurologic sequelae of mycoplasmal pneumonia.[17] Until now, to our knowledge the use cyclophosphamide has not been reported in the treatment of AHL. Its effect in this patient remains uncertain. Effective treatment probably consists of a combination of early diagnosis based on clinical suspicion, neuroimaging, brain biopsy, life support with reduction of elevated ICP in the critical stage, and early, sustained treatment with appropriate immunosuppressants.

References

1. Hurst EW. Acute hemorrhagic leukoencephalitis: a previously undefined entity. *Med J Aust.* 1941;2:1-6.

2. Beham PO, Moore MJ, Lamarche JB. Acute necrotizing hemorrhagic encephalopathy. *Postgrad Med.* 1973;54:154-160.

3. Byers RK. Acute hemorrhagic leukoencephalitis: report of three cases and review of the literature. *Pediatrics.* 1975;56:727-735.

4. Foley JM, Kane CA. Clinical pathologic conference. *Neurology.* 1957;7:135-141.

5. Coxe WS, Luse SA. Acute hemorrhagic leukoencephalitis: a clinical and electron-microscopic report of two patients treated with surgical decompression. *J Neurosurg.* 1963;20:584-596.

6. Gosztonyi G. Acute hemorrhagic leukoencephalitis (Hurst's disease). In: Vinken PJ, Brun GW, eds. *Handbook of Clinical Neurology.* Amsterdam, the Netherlands: Elsevier Science Publishers; 1978;3(pt 2):587-604.

7. Lander H. Acute hemorrhagic leukoencephalitis. *Australas Ann Med.* 1958;7:55-68.

8. Kulich SA. Acute hemorrhagic leukoencephalitis: report of a case and review of the literature. *Boston Med Q.* 1960;11:120-130.

9. Martins AN, Kempe LG, Harp GJ. Acute hemorrhagic leukoencephalitis with a concurrent primary herpes simplex infection. *J Neurol Neurosurg Psychiatry.* 1964;27:493-501.

10. Yesnick L. Central nervous system complications of primary atypical pneumonia. *Arch Intern Med.* 1956;97:93-98.

11. Fisher RS, Clark AW, Wolinsky JS, Parhad IM, Moses H, Mardiney MR. Postinfectious leukoencephalitis complicating *Mycoplasma pneumoniae* infection. *Arch Neurol.* 1983;40:109-113.

12. Rothstein TL, Shaw CM. Computerized tomography as a diagnostic aid in acute hemorrhagic leukoencephalitis. *Ann Neurol.* 1983;13:331-333.

13. Watson RT, Ballinger WE, Quisling RG. Acute hemorrhagic leukoencephalitis: diagnosis by computed tomography. *Ann Neurol.* 1984;15:611-612.

14. Levine S, Wenk EJ. A hyperacute form of allergic encephalomyelitis. *Am J Pathol.* 1965;47:61-88.

15. Lamarche JB, Behan PO, Segarra JM, Feldman RG. Recurrent acute necrotizing hemorrhagic encephalopathy. *Acta Neuropathol(Berl).* 1972;22:79-87.

16. Kristianson K, Harkmark W, Cohen MM. Acute hemorrhagic encephalitis. *Neurology (Minneap).* 1956;6:503-509.

17. Cotter FE, Bainbridge D, Newland AC. Neurological deficit associated with *Mycoplasma* pneumonia reversed by plasma exchange. *BMJ.* 1983;286:22.

Isolated Congenital Hemianopia Caused by Prenatal Injury to the Optic Radiation

Nicola K. Ragge, MRCP FCOphth; A. James Barkovich, MD;
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• Isolated congenital hemianopias are typically caused by developmental abnormalities of the occipital lobe cortex. We describe two patients with an incidental partial hemianopia associated with unilateral periventricular leukomalacia that was acquired prenatally. Magnetic resonance imaging scans suggest a late second or early third trimester unilateral cerebral ischemic event.

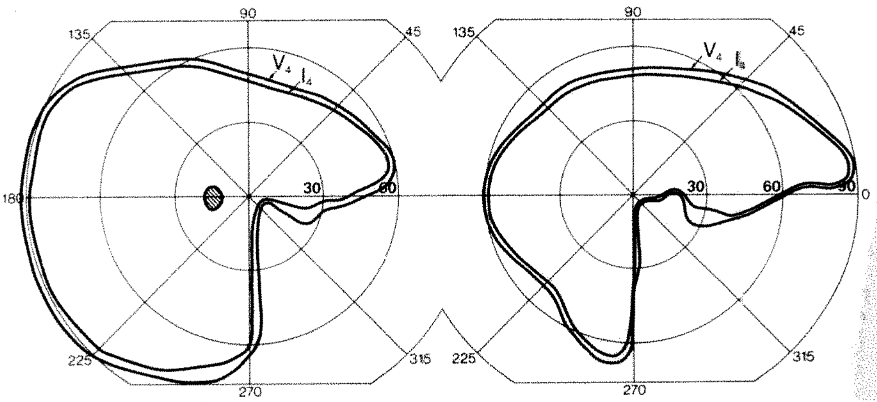
(*Arch Neurol.* 1991;48:1088-1091)

Isolated congenital occipital lesions with accompanying hemianopia usually involve gray and white matter. Examples include porencephaly[1-3]; vascular malformations, either isolated or in association with Sturge-Weber–type malformation without cutaneous signs[4]; colpocephaly[5]; and polymicrogyria of the striate cortex.[6,7] This report documents two cases of congenital hemianopia caused by prenatal injury to the periventricular white matter.

REPORT OF CASES

CASE 1.—A healthy 21-year-old white woman was found to have an inferior quadrantic field defect during a routine eye examination. She had a history of herpetic keratitis in her right eye. There was no history of prenatal or postnatal illness or neurologic disorder. Her visual acuities were 20/50 in the right eye and 20/20 in the left eye. There were no abnormalities of color vision. Her pupil reflexes were equal bilaterally. Both Goldmann and computerized visual field testing showed a right inferior homonymous quadrantanopia with minor incongruity along the horizontal meridian (Fig 1). There were signs in both retinas of nerve fiber loss corresponding to that seen in homonymous hemioptic atrophy.[8] Both discs were small in diameter. The right disc showed band atrophy, with loss of nerve fiber layer especially prominent at the nasal disc edge, where the pigment epithelial edge could be seen. The superior and inferior arcuate bundles were well preserved. On the left disc, a full complement of nasal nerve fiber layer could be seen, but temporal pallor and relative loss of the superior and inferior arcuate bundles

Fig 1.—Patient 1. Right inferior homonymous quadrantic defect demonstrated by Goldmann perimetry.



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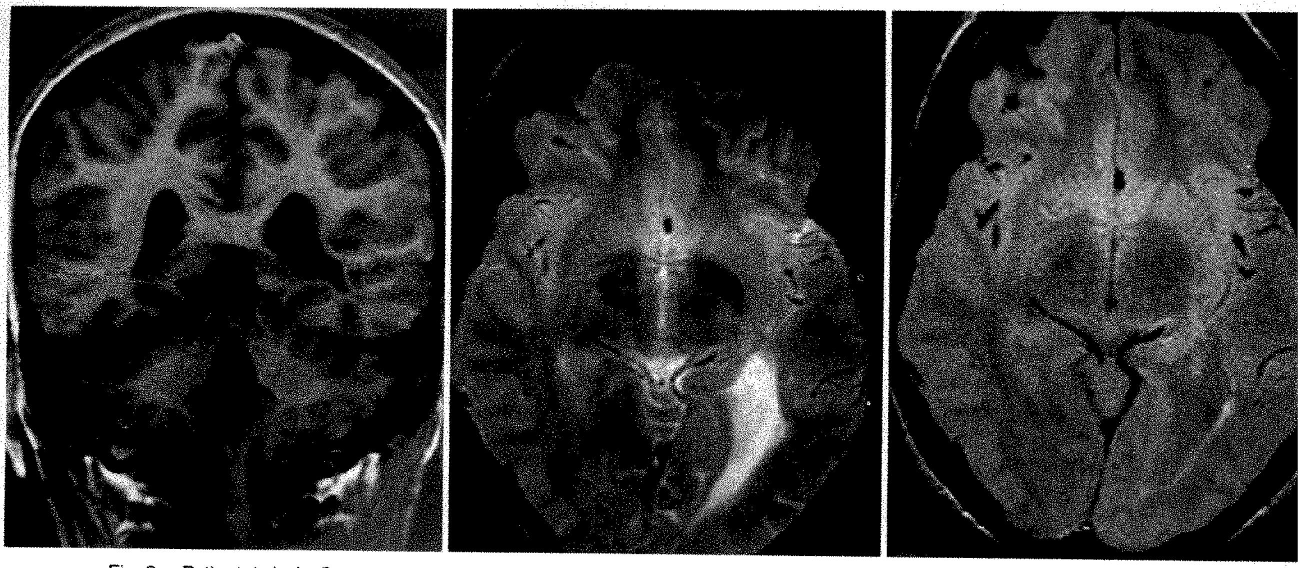

Fig 2.—Patient 1. Left, Coronal T_1-weighted image at the level of the ventricular trigone shows a nearly complete absence of periventricular white matter inferolaterally on the left. The depths of the cortical gyri nearly abut the ventricular surface. Center, Heavily T_2-weighted axial image shows the expanded trigone and paucity of periventricular white matter. The lateral margin of the ventricle is poorly defined. Right, Spin-density image at the same level as center shows high signal intensity in the periventricular white matter, representing damaged tissue. The presence of this area of high intensity indicates that the damage occurred later than that in patient 2 (compare with Fig 4, right).

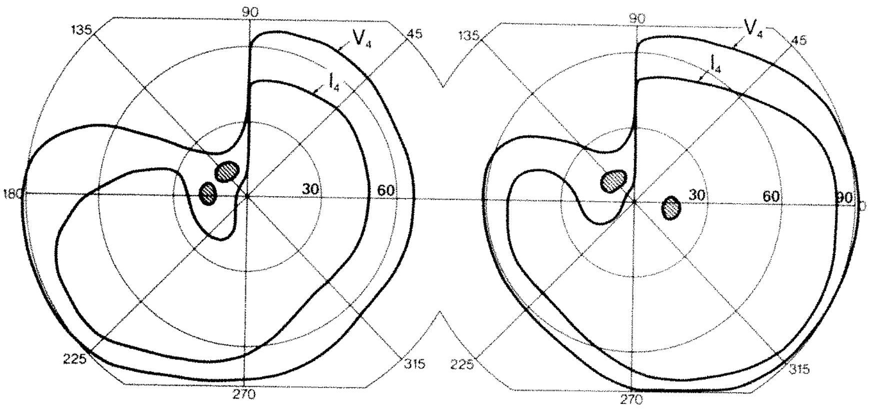

Fig 3.—Patient 2. Left superior homonymous quadrantic defect demonstrated by Goldmann perimetry.

were present.

Magnetic resonance images of the brain (Fig 2) showed ex vacuo enlargement of the trigone and occipital horn of the left lateral ventricle. The close approximation of the cortical gyri, particularly the posterior insular cortex, to the ventricular surface was characteristic of the pattern seen as a result of loss of the intervening white matter. In this location, the white matter is partially composed of the optic radiations. T_2-weighted images showed a thin strip of high signal intensity in the immediate periventricular white matter indicative of replacement of normal tissue by gliotic white matter.

Case 2.—A healthy 10-year-old black boy, vho was being followed up in the eye clinic 'or a left esotropia and amblyopia, was found o have a left homonymous hemianopia. 'here was no significant obstetric or perina-al history. His visual acuities were 20/25 in ie right eye and 20/200 in the left eye. The pupils were 3 mm in diameter, equal, and fully reactive. There was a mild left relative afferent pupillary defect. The patient had a left superior homonymous quadrantanopia (Fig 3). The retinal nerve fiber layer demonstrated a pattern of nerve fiber loss indicating homonymous hemioptic atrophy.[8] The remarkable feature of both discs was that they were large in diameter, with pronounced physiological cups and a nasal entrance of the vessels. The left disc was vertically oval and kidney shaped with band atrophy. There was an atrophic nerve fiber layer at the nasal border of the left disc compared with a full nasal nerve fiber layer adjacent to the right disc.

Computed tomography of the head showed enlargement of the right lateral ventricle, most notably the trigone, as a result of loss of periventricular white matter. Magnetic resonance imaging with gadolinium-pentetic acid (Fig 4) showed the same enlargement of the ventricle and more clearly showed t close approximation of the depths of the c tical gyri to the ventricular wall. T_2-weight images showed normal intensity of the pe ventricular white matter. No enhanceme was seen after administration of intravenc contrast.

COMMENT

We have described two cases of u lateral white matter injury in the regi of the optic radiations causing isolat partial hemianopias. In both cases t ophthalmologic evidence of transsyna tic nerve fiber degeneration establish the occipital injury as a prenat event.[8,9] The occurrence of such notic able retinal nerve fiber layer and opt disc changes is somewhat unexpecte the predicted loss of nerve fibers l transsynaptic degeneration from a l sion that causes a quadrantanop would be about 25% from each opt nerve. We have no explanation for t fact that both patients' homonymou field defects were quadrantic, while t magnetic resonance imaging sca showed diffuse, not focal, thinning the visual radiation in the involved o cipital lobes.

The affected regions of both brai have magnetic resonance imaging cha acteristics that fit those reported f end-stage periventricular leukomal cia.[10,11] These are (1) ventriculomegal sometimes with irregular outline of th ventricular surface; (2) reduce amounts of periventricular white ma ter at the trigone and, in more seve cases, the entire centrum semiovale; (

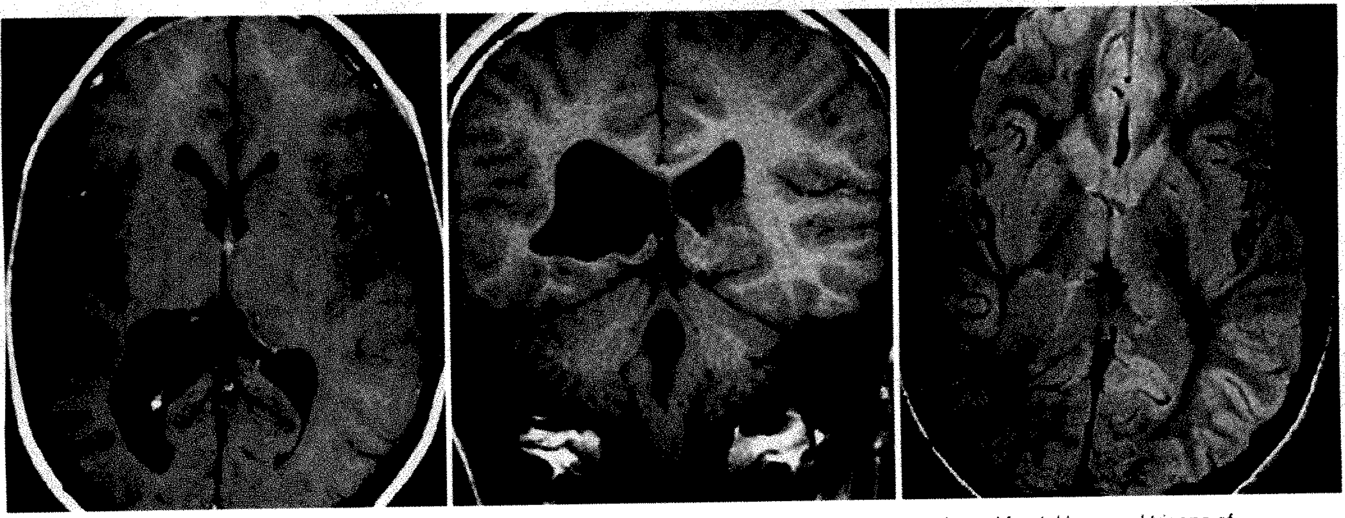

Fig 4.—Patient 2. Left, Axial T_1-weighted image after infusion of intravenous contrast shows enlarged frontal horn and trigone of the right lateral ventricle. Note the paucity of white matter between the cortical gyri and the ventricular surface on the right side compared with the left. No contrast enhancement is apparent. Center, Coronal T_1-weighted image at the level of the ventricular trigones shows that the absence of periventricular white matter is more marked inferiorly at the level of the optic radiations. Right, Axial spin-density image at the level of the ventricular trigones shows an absence of high signal intensity in the periventricular white matter (compare with Fig 2, right). This implies an earlier gestational event.

deep and prominent cortical sulci with subcortical white matter approaching the ventricles with little interposed white matter; and (4) prolonged T_2 relaxation time in the immediate peritrigonal white matter, sometimes extending anteriorly along the ventricular body.

Periventricular leukomalacia occurs most commonly in premature infants who also have other complications including hyaline membrane disease, persistent fetal circulation, and germinal matrix hemorrhage.[12,13] Both pathological and neuroimaging studies have shown a characteristic progression that begins with edema, followed by coagulation necrosis and eventually cavitation, usually in 3 to 6 weeks.[12-14] The cysts usually collapse, the affected brain exhibiting gliosis and reduction in the quantity of white matter in the periventricular region. The ependymal separation between the cavities and the ventricle may break down, with consequent incorporation of the cavities into the ventricle.

Since periventricular leukomalacia occurs most commonly in the peritrigonal region,[15] through which the geniculocalcarine radiations course, it is not surprising that patients with this condition commonly have visual impairment.[16,17] However, this is usually seen in the context of a premature infant with bilateral defects. Several authors have described unilateral periventricular leukomalacia[18-21]; however, all have concentrated on motor dysfunction and none have described visual impairment.

The pathogenesis of most cases of periventricular leukomalacia is now widely accepted as being the result of ischemia in the immature brain.[11,22,23] The "watershed areas" of the premature brain are located in the periventricular region.[24] At about 36 weeks' gestational age, the watershed areas begin to move peripherally, eventually reaching the subcortical white matter and cerebral cortex at term. It is a logical extension of this concept to postulate that unilateral periventricular leukomalacia is most likely to be the result of in utero hypoperfusion of a single hemisphere.

Gilles et al[25] have shown that the glial response to brain injury is minimal prior to about 26 weeks' gestational age. Barkovich and Truwit[11] have further shown that asphyxic brain injury prior to 28 weeks' gestational age shows minimal periventricular T_2 prolongation. The area of prolonged T_2 relaxation time adjacent to the enlarged trigone in patient 2 indicates an injury between about 28 and 34 weeks' gestational age, whereas the absence of periventricular prolonged T_2 relaxation in patient 1 indicates an earlier injury, most likely during the second half of the second trimester.

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References

1. Remillard GM, Ethier R, Andermann F. Temporal lobe epilepsy and perinatal occlusion of the posterior cerebral artery: a syndrome analogous to infantile hemiplegia and a demonstrable etiology in some patients with temporal lobe epilepsy. *Neurology.* 1974;24:1001-1009.

2. Hoyt WF. Congenital occipital hemianopia. *Neuro-ophthalmol Jpn.* 1985;2:252-259.

3. Novakovic P, Taylor DSI, Hoyt WF. Localising patterns of optic nerve hypoplasia—retina to occipital lobe. *Br J Ophthalmol.* 1988;72:176-182.

4. Andriola M, Stolfi J. Sturge-Weber syndrome: report of an atypical case. *AJDC.* 1972;123:507-510.

5. Garg BP. Colpocephaly: an error of morphogenesis? *Arch Neurol.* 1982;39:243-246.

6. Tychsen L, Hoyt WF. Relative afferent pupillary defect in congenital occipital hemianopia. *Am J Ophthalmol.* 1985;100:345-346.

7. Taylor DC, Falconer MA, Bruton CJ, Corsellis JAN. Focal dysplasia of the cerebral cortex in epilepsy. *J Neurol Neurosurg Psychiatry.* 1971;34:369-387.

8. Hoyt WF, Rios-Montenegro EN, Behrens MM, Eckelhoff RJ. Homonymous hemioptic hypoplasia: fundoscopic features in standard and red-free illumination in three patients with congenital hemiplegia. *Br J Ophthalmol.* 1972;56:537-545.

9. Miller NR, Newman SA. Transsynaptic degeneration. *Arch Ophthalmol.* 1981;99:1654.

10. Flodmark O, Lupton B, Li D, et al. MR imaging of periventricular leukomalacia in childhood. *AJNR.* 1989;10:111-118.

11. Barkovich AJ, Truwit CL. Brain damage from perinatal asphyxia: correlation of MR findings with gestational age. *AJNR.* 1990;11:1087-1096.

12. Volpe JJ. Hypoxic-ischemic encephalopathy: neuropathology and pathogenesis. In: *Neurology of the Newborn.* 2nd ed. Philadelphia, Pa: WB Saunders Co; 1987:209-235.

13. Friede RL. *Developmental Neuropathology.* 2nd ed. New York, NY: Springer-Verlag NY Inc; 1989:69-97.

14. De Reuck J, Chattha AS, Richardson EP. Pathogenesis and evolution of periventricular leukomalacia in infancy. *Arch Neurol.* 1972;27:229-236.

15. Banker BQ, Larroche J-C. Periventricular leukomalacia of infancy. *Arch Neurol.* 1962;7:386-410.

16. Lambert SR, Hoyt CS, Jan JE, Barkovich AJ, Flodmark O. Visual recovery from hypoxic cortical blindness during childhood: computed to-

mography and magnetic resonance imaging predictors. *Arch Ophthalmol.* 1987;105:1371-1377.

17. Flodmark O, Jan JE, Wong PKH. CT of the brains of children with cortical visual impairment. *Dev Med Child Neurol.* 1990;32:611-620.

18. Wiklund L-M, Uvebrant P, Flodmark O. Morphology of cerebral lesions in children with congenital hemiplegia: a study with computed tomography. *Neuroradiology.* 1990;32:179-186.

19. Molteni B, Oleari G, Fedrizzi E, Bracchi M. Relation between CT patterns, clinical findings and etiological factors in children born at term, affected by congenital hemiparesis. *Neuropediatrics.* 1987;18:75-80.

20. Claeys V, Deonna T, Chrzanowski R. Congenital hemiparesis: the spectrum of lesions. *Helv Pediatr Acta.* 1983;38:393-455.

21. Kotlarek F, Rodewig R, Brull D. CT findings in congenital hemiparesis in childhood and their relation to etiology and prognosis. *Neuropediatrics.* 1981;12:101-109.

22. Pape KE, Wigglesworth JS. *Haemorrhage, Ischaemia, and the Perinatal Brain.* Philadelphia, Pa: JB Lippincott; 1979;69/70. Clinics in Developmental Medicine.

23. Wiklund L-M, Uvebrant P, Flodmark O. CT as an adjunct in etiological analysis of hemiplegic cerebral palsy. *Neuropediatrics.* In press.

24. Takashima S, Tanaka K. Development of cerebrovascular architecture and its relationship to periventricular leukomalacia. *Arch Neurol.* 1978;35:11-16.

25. Gilles FH, Averill DR Jr, Kerr C. Changes in neonatally induced cerebral lesions with advancing age. *J Neuropathol Exp Neurol.* 1977;36:666-684.

Visual Hallucinations and Racing Thoughts on Eye Closure After Minor Surgery

C. Miller Fisher, MD

• Two hours after minor surgery under local anesthesia, a 67-year-old man developed vivid visual hallucinations that were present only when he closed his eyes. After lasting 4 hours, the hallucinations were succeeded by racing thoughts, lasting 2 hours, and then by illusionary movements of his body. The reaction was attributed to the effect of lidocaine. The case resembles one previously reported.

(*Arch Neurol.* 1991;48:1091-1092)

The occurrence of visual hallucinations on eye closure in a fully alert patient is a rarely reported phenomenon. Recently, one case was described in which the hallucinations were attributed to atropine toxicity and lasted 11 days.[1] The present case bears a close resemblance; but, in addition to visual hallucinations, the patient experienced "racing thoughts" (his term) and hallucinations of body movement on eye closure. The symptoms began shortly after a minor operation that was performed under local anesthesia.

Abnormal mental events are of interest, not only as they aid in clinical interpretation, but also as they extend our knowledge of the brain's behavioral capability.

REPORT OF A CASE

A 67-year-old hypertensive physician reported a 15-minute spell of weakness of the right side of the face and the right hand. Results of neurological examination were normal, as was a cranial computed tomographic scan. Angiography showed stenosis of both internal carotid arteries to less than -mm residual lumen, worse on the right side. A right-sided carotid endarterectomy was attempted, but patency could not be restored, and the internal carotid artery was ligated. Immediate recovery was uneventful; but, 24 hours later, on removing the drain from the wound, bleeding occurred into the neck, forming a mass that displaced the trachea. The blood clot was promptly evacuated using 15 mL of 0.01% lidocaine, with 0.005% phenylephrine hydrochloride as the local anesthetic. The only additional medications were codeine, 60 mg, given orally 2 hours before the operation; cefazolin sodium, 1 g; and labetalol, 5 mg, administered twice during the procedure, which was uncomplicated and lasted about 1 hour. Cerebral hypoxia did not occur. The labetalol temporarily replaced atenolol, which the patient had been taking for about 6 years.

At 12:30 PM, two hours after surgery, while drowsing, the patient began to experience visual hallucinations; these continued for about 4 hours. According to his daughter, who sat at his bedside as he described the events to her, he was lucid and appropriate at all times. He was first seen by me a few hours after the aberrant ideation had ceased; at this time, his memory of the happenings was still fresh.

The visual hallucinations consisted of four main topics: books and other printed material, street scenes, snowy landscapes, and animals of many kinds. The images followed one another in quick succession, "nonstop with no rhyme or reason," each one lasting 2 or 3 seconds. When he opened his eyes, the visions disappeared. Although he was wide awake and apparently clear mentally, it was for some reason difficult to keep his eyes open. "It was as if they were being forced shut." He was not frightened or alarmed, but was restless and unduly excited; he attributed this to a feeling of being out of control and helpless. The images were colored and projected into the center of space before him, without lateralization. They were silent, and figures showed no facial movements to suggest that they were speaking. The individual hallucinations were entirely unrelated to one another, with no recognizable narrative connection. It was broad daylight, and the room was brightly lit.

The printed matter consisted of books and pages; in addition, handwritten material was present. The colored street scenes were not recognized as being in any particular city; many people about 1 m tall were rushing across the street from side to side at great speed, dashing hither and thither, creating a bewildering confusion. The streets were lined with buildings on each side. The people seemed to be further away than the surroundings, creating the appearance of miniaturization. There were no autos. The snow scenes stretched for miles over low hills. As the hospitalization was in the winter time, when there was snow, this may have been a determining factor; but, a snow scene could quickly be followed by one without snow. There were no trees. The animals were deformed and repugnant; for example, there were ugly, one-eyed Picasso-like monsters, or, grotesque, nongeometrical shapes that were everchanging. The animals were stationary, as in a picture. There were no recognizable normal animals, such as dogs, cats, horses, or rodents. The coloring was mostly of water colors and pastels, except for white, which was quite bright, and orange, which was vivid.

As the visual hallucinations subsided, they were followed by a most unpleasant episode of "racing thoughts." The patient was not aware of any visual or auditory images. Unconnected thoughts followed one another in quick succession, without any sense. They passed so swiftly, the patient was unable to recognize them. It was his impression that they were about people, rather than things or places. They probably involved family members, including a grandson. Each thought might consist of three staccato bits, only to be interrupted by an entirely different thought with its own few bits, with the whole series being fragmentary and meaningless. Also, the thinking spree was present only when his eyes were closed; this was immediately dispelled on opening the eyes; but, again, there was difficulty in keeping the eyes open in the absence of sleepiness. The episode of rushing thoughts was stranger and more unpleasant than the visual hallucinations, although the thoughts themselves were not frightening or bizarre. The patient agreed that the thoughts might have been ordinary thinking, speeded up to a dizzying degree. In light of the patient's statement

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that his "racing thoughts" were without visual or auditory imagery, the presence of imagery during normal thinking was discussed with him. He concluded that the thoughts passed and changed so rapidly that analysis was impossible. The "racing thoughts" preempted his mind, precluding any parallel thinking on his own.

In the minutes following cessation of the "racing thoughts" that had lasted about 2 hours, the patient had the sensation that both he and his bed were moving along in the direction of the foot of the bed. Alarmed, he would open his eyes and seize the side rails of his bed, whereupon the feeling of movement stopped. The bed was involved in the movement, and not just the patient; nevertheless, the act of holding on (or opening the eyes) stopped the sensation. He thought the movement resembled his being taken to the operating room on a stretcher; that is, the speed of the motion was similar. Each time he closed his eyes, the sensation recurred. This lasted for 30 minutes to 1 hour.

The patient was aware that all of the phenomena described were in his imagination and not real. He opened his eyes deliberately and looked around to be sure that this mind was clear. According to his daughter, his speech was normal. The patient's neurologic examination results were normal, both before and after the surgical procedure. His memory of the details was quite intact, indicating that the hippocampal memory system was recording events. The visual hallucinations were highly complex, evidence that the visual association cortex maintained a high-level performance.

COMMENT

A previous article[1] reported the occurrence of visual hallucinations associated with eye closure in a patient with atropine toxicity. The visual hallucinations in the present case were much the same—present on eye closure and consisting of a rapid succession of unrelated images, faintly colored, and silent. The two cases probably represent the same process. In the atropine case, the hypothesis was advanced that if a parallel with any recognized normal neurologic phenomenon was to be drawn, it was with the hypnagogic hallucinations of sleep onset. It was speculated that the hallucinations were the result of a primary disturbance in the sleep-awake apparatus of the brain stem—in particular, in the rapid eye movement system of the pontine tegmentum. Support for the hypothesis was limited to clinical observations—the crucial importance of eye closure, a disturbance of sleep, excessive dreaming, and the presence of a dreamlike quality in some of the visual hallucinations. In the present case, the entire abnormal period lasted only 7 hours, although the patient may have slept in the interval between completion of surgery and the onset of hallucinations. When asked why he closed his eyes rather than keeping them open, thus preventing the imagery, the patient's answer was of some interest. His explanation was that for some reason it was difficult to keep them open. Eye closure is a central feature of the syndrome, and if in some way it is "forced," a relationship with sleep would be strengthened.

Besides visual hallucinations, the present patient had the two additional features: racing thoughts and illusions of movement, occurrence of which was also strictly related to eye closure. It may be presumed that these features share a common or closely related origin with the visual hallucinations and that all three are analogous manifestations. The racing thoughts showed the same nonstop rapid turnover of unrelated items, as did the visual hallucinations. Racing thoughts and illusory movement are not described in hypnagogic experience,[2] and racing thoughts do not occur in dreaming. In this regard, the stated hypothesis is weakened.

The symptom of racing thoughts is rare in neurology. The manic phase of manic-depressive illness may bring a "press of speech and ideas." Schizophrenics may show the same trait, but whether there is any parallel with the present symptom requires further observation. The records of the Massachusetts General Hospital Stroke Service contained notes on one patient whose story may be relevant. A 50-year-old man with an upper respiratory infection and a temperature of 40°C reported visual hallucinations of objects, buildings, and magnificent cathedral arches on closing his eyes. The images lasted only 1 to 2 seconds, were in black and white, full size, and about 6 m distant. The images seemed to change or shift when the eyes moved beneath the closed lids. They were always superimposed on a grid or meshwork containing interstices, but not a woven texture. There was no sound or color. The hallucinations disappeared on opening the eyes. Also, on closing the eyes, the patient had what he called, "forced ideas," in which he thought about things that were foreign to him, as well as threatening. He said "they were vivid dreams, but not visual."

Just as visual hallucinations, in view of their complex nature most likely arise in the visual association cortex, racing thoughts must be a cortical phenomenon, localized probably in the association areas of the dominant parieto-occipital region. In keeping with this, is the occurrence of brief runs of racing thoughts in partial complex seizures of temporal lobe origin.

The term *illusionary movement* used for the patient's third symptom is probably inaccurate, for the sense of motion with the eyes closed was a false perception; therefore, this qualifies as a hallucination, rather than as an illusion. A false sense of turning or rocking is common in labyrinthine disorders when the eyes are closed, but the occurrence of a well-patterned discrete motion, such as our patient described, is outside our personal neurologic experience. The nature of the false-linear motion of the body and its locus within the nervous system are quite unknown. By analogy with the other two symptoms, a cortical origin would be suspected.

Whereas atropine was held to be the responsible agent in the previous case, it was not a factor here. Lidocaine is commonly associated with sleepiness and confusion,[3] and it must be the primary suspect. Labetalol in two doses of 5 mg can hardly be incriminated, although β-adrenergic blockers can cause confusion.[4] Cefazolin is not known to be toxic to the central nervous system. Phenylephrine in very small doses is an unlikely offender. At the same time as a toxic effect of medication is emphasized, it is to be recalled that in the supplementary case described, infection and fever produced a somewhat similar syndrome. It is of interest that one of the main adverse effects of lidocaine is drowsiness, reflecting an action in the sleep-awake system, wherein, by present postulate, the patient's symptoms arose. If that is true, the clinical picture illustrates the principle that toxic manifestations originate within a distinct functional subsystem of the brain, here, the sleep-awake subsystem.

One other point warrants comment, namely, the visualization of printed and written material in hallucinations. Whereas in the present case no meaning could be discerned, in the previous case, the patient thought he recognized words and meaning; but, on peering closely, the letters became nondescript markings and, finally, disappeared altogether. Meaningful print and script do not appear in dreams, indicating that the brain cannot display from memory preformed written material that can be visualized.

References

1. Fisher CM. Visual hallucinations on eye closure associated with atropine toxicity: a neurological analysis and comparison with other visual hallucinations. *Can J Neurol Sci*. 1991;19:18-27.

2. Vihvelin H. On the differentiation of some typical forms of hypnagogic hallucinations. *Acta Psychiatr Neurol*. 1948;12:359-389.

3. *Physicians Desk Reference*. 42nd ed. Oradell, NJ: Edward R Barnhart, Publisher; 1988:625.

4. Frishman WH. β-Adrenergic receptor blockers: adverse effects and drug reactions. *Hypertension*. 1988;11(suppl 2):21-24.

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Professional Opportunities

CHARLOTTE, NORTH CAROLINA: High quality group of five neurologists, all of whom are subspecialized, seeks to add a well-trained specialist. Contact: Mike Kaufman, MD, 1900 Randolph Road, Suite 1010, Charlotte, NC 28207. Or call: (704) 334-7311.

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EXCELLENT OPPORTUNITY for BC/BE neurologist to join 80-physician comprehensive, multispecialty group in San Francisco Bay Area. Large, varied referral base from Pediatrics, IM, FP, and Surgery. EMG/NCV, EEG, Evoked Response Testing, CT, MRI, Radiology support all available on site. Opportunity to interface with specialists of all types including neurosurgeons. Major university teaching affiliation encouraged and possible. Close proximity to 400-bed full service, modern hospital serving population of 300,000. Competitive guaranteed salary with bonus productivity plan for initial 18 months leading to partnership track. Extensive benefit package including housing incentives. Unique cultural, recreational and educational opportunities. Send CV to: Gary D. Zweig, MD, Recruitment Chairman, Sunnyvale Medical Clinic, P.O. Box 3496, Sunnyvale, CA 94088-3496.

OCHSNER NEUROLOGIST — The Ochsner Clinic of Baton Rouge seeks qualified neurologists to expand its department in our multi-specialty regional clinic. The practice offers an opportunity to practice in a setting which supports innovation and involvement in education and research. Competitive salary and excellent fringe benefits program. Send CV to: Ochsner Clinic of Baton Rouge, Physician Recruiting Support Services, 16777 Medical Center Drive, Baton Rouge, LA 70816; or call: (800) 488-2240.

NEUROLOGIST: Urban area in North Carolina. BC/BE, to join solo neurologist in a rapidly expanding, progressive and active practice. All neurodiagnostic modalities available. Excellent salary leading to partnership. Experience in EMG, EEG and EPs. Please reply with CV to: Box #822, c/o AON.

EXCELLENT OPPORTUNITY for BC/BE neurologist to practice in large eastern metropolitan area. Opening for July 1992 or earlier, for private practice with geographic full-time appointment at large teaching institution. Medical school appointment, teaching and research opportunities. Subspecialty in movement disorders, muscle diseases or neuro-oncology preferred but not required. Submit CV to: P.O. Box 5849, Pittsburgh, PA 15209-0849.

NEUROLOGIST: BC/BE neurologist to join established neurologist or establish independent practice with shared call and negotiable reimbursement options. Progressive midwestern community hospital close to several academic institutions and with attractive recreation options. Contact: B. Sisman, MD, (313) 242-6030.

NEUROLOGIST — Reynolds Army Community Hospital, Fort Sill, Oklahoma is currently seeking BE/BC neurologist. Opportunity to practice in new state-of-the-art clinic office/hospital setting. Competency in EEG/EMG required. CAT scan and MRI interpretation experience desirable. No capital investment required. Compensation is negotiable depending on applicant's qualifications. Information, application forms and instructions for applying may be obtained by calling or writing the: Department of the Army, Commander, USAMEDDAC, Attention: HSUA-CAM, Major Condra, Fort Sill, OK 73503-6300. Telephone number: (405) 351-4021/2418.

Professional Opportunities

THE OCHSNER CLINIC in New Orleans is seeking a BE/BC neurologist with fellowship-training in neuromuscular disease. The candidate should have strong clinical skills in the diagnosis and management of both peripheral nerve and muscle disease. Experience in interpreting nerve and muscle biopsy is also required. It would be preferred yet not essential that the physician be able to perform the actual biopsy. The Ochsner Clinic is a large (250 MDs) multi-specialty clinic with an adjoining 500-bed hospital. The neurology service is affiliated with the Tulane University Neurology Department and our staff have clinical appointments at Tulane University. The neurology service has teaching responsibilities at the Ochsner Foundation Hospital for Tulane neurology residents, Ochsner medicine residents, Louisiana State University Rehabilitation residents, Ochsner interns and Tulane medical students. At Ochsner there are also opportunities for individual and cooperative clinical research. Interested physicians should send a complete CV to: Dr. Richard L. Strub, Chairman, Department of Neurology, Ochsner Medical Institutions, 1514 Jefferson Highway, New Orleans, LA 70121. For more details, please call: (800) 488-2240.

NEUROLOGIST — San Francisco, Lake Tahoe and Reno are just 90 minutes away. Neurologist to join one other in busy and diverse practice. The groups well established referral network of 45 physicians and surgeons will insure volume and variety of cases. Department is equipped with EMG, EEG, and CT. Sacramento is a brief 35 minute drive. For complete details: Gerry Myers (800) 368-2416, Extension 107.

GREAT LAKES! Well-established, rapidly growing neurology practice seeks additional BC/BE neurologist. Charming community in area nationally recognized for medical excellence. Country lifestyle yet easily accessible to major metropolitan area. State-of-the-art facilities; good patient mix; coverage from BC neurologists; financial/benefit package commensurate with experience. Contact: Ruth Koch, (800) 368-2416, Extension 104.

SEATTLE — Expanding, 68-physician, multispecialty group seeking sixth BE/BC neurologist-subspecialty training preferred. Options for academic affiliation. Epilepsy, stroke, geriatrics, electrophysiology and movement disorder are areas of need. Send CV to: The Polyclinic, Attention: Robert Schroeder, Administrator, 1145 Broadway, Seattle, WA 98122-4299.

THE DEPARTMENT OF NEUROLOGY at Henry Ford Health Sciences Center is looking for BC/BE clinical neurologists with expertise in electromyography and electroencephalography to join a very active clinical neurophysiology section where over 10,000 studies are performed annually. Qualified individuals are expected to teach Neurology residents (inpatient and outpatient), participate in training of residents and fellows in clinical neurophysiology, and work cooperatively in a 20-neurologist department. Research opportunities and facilities exist in a number of related areas including MEG. Contact: K.M.A. Welch, MD, William T. Cossett Chair, Department of Neurology, Henry Ford Hospital, 2799 West Grand Boulevard, Detroit, MI 48202.

NEUROLOGIST — The Cleveland VA Medical Center is recruiting for a part-time (5/8) position for a neurologist. The applicant must be board-certified or board-eligible in neurology, have expertise in both EMG and EEG and satisfy requirements for appointment in the Neurology Department at Case Western Reserve University. Responsibilities include attending neurology outpatient clinics in Youngstown, Canton, Brecksville, and Cleveland, Ohio, in addition to his/her responsibility for inpatient, consult services, reading EEGs and performing EMGs. Interested individuals should contact: Thomas R. Claflin at (216) 526-3030, Extension 7916. Or send a resume to his attention: Personnel Service 05(B), VAMC, 10000 Brecksville Road, Brecksville, OH 44141. The Cleveland VAMC is proud to be an equal employment opportunity employer.

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Professional Opportunities

METROPOLITAN NEW YORK CITY — BC/B neurologist to join solo general practice. EMG EP/EEG experience preferred. Excellent financia package. University affiliation. Send CV to: Alla Perel, MD, 1055 Hylan Boulevard, Staten Island, N 10305.

Positions Available

NEW ENGLAND SEACOAST COMMUNITY seek second neurologist for community hospital prac- tice. Excellent location with abundant outdoo recreation, good schools, major scientific institu tions nearby. First year salary with early partnersh option. Please contact: Michael Leahy, MD, Bramblebush Park, Falmouth, MA 02540.

NEUROLOGIST: BC/BE. Must have skills in EEG, EMG and evoked potentials. To be associated wit two neurologists in private practice, in a medica center location, with a expanding modern 181-bed hospital with complete modern equipment, and all specialties are represented. Situated in an attractive high desert area of the northwest with abundan recreational activities including the finest skiing, hiking, hunting, and fishing. Excellent schools available, both public and private. This is a very active practice in a drawing area of 175,000 and an excellent opportunity. Reply with curriculum vitae to: Bo #823, c/o AON.

Faculty Positions

BE/BC NEUROLOGIST, subspecialty expertis neuro-oncology, including chemotherapy, resear and teaching. Assistant Professor with tenure earning option. Salary and benefits negotiable. November 1, 1991 start. Contact: Leon D. Prockop, MD, Chairman Neurology Department, (813) 974-2794. University of South Florida is an affirmative action/equal opportunity employer.

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Faculty Positions

ACADEMIC NEUROLOGIST sought with fellowship training in neuromuscular diseases and EMG. Opportunity to develop research program, teach neurology residents, and start a fellowship. State-of-the-art equipment and technician furnished. Nerve and muscle biopsy laboratory available in the department. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

ACADEMIC NEUROLOGIST sought with competence in sleep disorders to direct sleep center. Opportunity also in epilepsy, EEG, and evoked potentials, teach neurology residents and students. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

ACADEMIC NEUROLOGIST sought with training in cerebrovascular disease to develop program. Collaborate with neuropathology and radiology to develop research. Teach neurology residents. Reply with CV to: Joseph B. Green, MD, Chairman, Department of Medical and Surgical Neurology, Texas Tech University Health Sciences Center, Lubbock, TX 79430. Texas Tech University is an equal opportunity employer.

ACADEMIC NEUROLOGIST: A full-time academic position is available at the Assistant Professor level at Vanderbilt University Medical Center. Candidates should be board-certified/board-eligible in neurology and should have completed two years of full-time fellowship in epilepsy and clinical neurophysiology. The position includes teaching responsibilities and research. The preferred candidate will have experience in clinical epilepsy, long-term monitoring, electrocorticography, and experimental drug studies. Interested individuals should send CV to: Bassel Abou-Khalil, MD, Department of Neurology, Vanderbilt University Medical Center, 2100 Pierce Avenue, Room 336, Nashville, TN 37212.

Faculty Positions

THE DEPARTMENT OF NEUROLOGY at The University of Iowa is recruiting a full-time faculty member (Assistant Professor level) to join two other members in the Division of Cerebrovascular Diseases. The Division of Cerebrovascular Diseases has an active program in education, patient care, and research, and is leading a large multi-center clinical trial in acute stroke therapy. Appointees are expected to join in the Division's activities and to conduct an independent program of scientific investigation. The new faculty member should be qualified to practice medicine in Iowa, board-certified or -eligible in neurology, and have had additional training, preferably through a fellowship, in cerebrovascular disease. Please send inquiries to: Antonio R. Damasio, MD, Professor and Head, Department of Neurology, University of Iowa, Iowa City, IA 52242. The University of Iowa is an equal opportunity, affirmative action employer. Women and minorities are encouraged to apply.

THE SCHOOL OF MEDICINE of the University of Missouri Health Sciences Center is seeking applications and nominations for the position of Professor and Chairperson of the Department of Neurology. The candidate must have senior academic experience with commitment to education and research. Demonstrated leadership and administrative capabilities are essential. The Chair is responsible for recruitment and retention of faculty, education of medical students and residents, the development of research programs and the Neurology clinical services in the University Hospital and Clinics. Send applications to: Donald H. York, PhD, Chair, Neurology Search Committee, University of Missouri-Columbia, School of Medicine, Office of the Dean, Columbia, MO 65212. The University of Missouri-Columbia is an equal opportunity and affirmative action institution. Females and minorities are encouraged to apply.

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Residencies

NEUROLOGY RESIDENCY PROGRAM at the University of North Carolina. PGYII position available for entrance into Neurology Residency Program for 1992. Appointment will be made through the Neurology Residency Matching Program in 1992. Our program offers strong clinical training in general adult and child neurology as well as subspeciality exposure to epilepsy, sleep disorders, neuromuscular diseases and pain. For information contact: John A. Messenheimer, MD, School of Medicine, Department of Neurology, University of North Carolina, CB #7025, 751 Clinical Sciences Building, Chapel Hill, NC 27599-7025. (919) 966-3707.

THE UNIVERSITY OF Cincinnati Neurology Department is offering a second year neurology residency position (PGY III) beginning as soon as possible. For information contact: Joseph P. Broderick, MD, Residency Director, Department of Neurology, University of Cincinnati Medical Center, Cincinnati, OH 45267-0525. (513) 558-5431.

Fellowships

FELLOWSHIP IN CEREBROVASCULAR disease: Fellowships in cerebrovascular disease are available in the Department of Neurology at the University of Iowa. Comprehensive clinical training in diagnosis and management of patients with stroke is complemented by opportunities for clinical or basic research. Fellows are active participants in patient care and collaborate in several on-going local and multi-center clinical research studies. Candidates should be board-eligible or -certified in neurology and licensed to practice medicine in the United States. Please send inquiries to: Harold P. Adams, Jr, MD, Division of Cerebrovascular Diseases, Department of Neurology, University of Iowa, Iowa City, IA 52242; or call: (319) 356-4110. The University of Iowa is an affirmative action, equal opportunity employer. Women, minorities, and handicapped are encouraged to apply.

NATIONAL STROKE ASSOCIATION announces career-development fellowship awards ($30,000/year) for stroke research. Application due January 15, 1992 for July 1992 commencement. Contact: National Stroke Association, 300 East Hampden Avenue, #240, Englewood, CO 80110. (303) 762-9922.

PAIN FELLOWSHIP — The Pain Service in the Department of Neurology at Memorial Sloan-Kettering Cancer Center is seeking a board-eligible/board-certified neurologist for a pain fellowship. This is a one or two year position which offers comprehensive training in pain evaluation and treatment with a strong emphasis on cancer pain. Fellows will participate in clinical investigations of neuro-oncologic pain syndromes and the pharmacology of opioid analgesics. Laboratory research opportunities directed at the mechanisms of opiate action and the molecular pharmacology of opiate receptors are also available. Please contact: Kathleen M. Foley, MD, Department of Neurology, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, New York, NY 10021.

NEURO-ONCOLOGY Fellowships/Instructorships: July 1992 and 1993 — Neuro-oncology fellowships/instructorships are available for July 1992 and 1993. The University of California, San Francisco, Department of Neurological Surgery, Neuro-Oncology Service, offers unprecedented opportunities to participate in chemotherapy and radiation therapy trials of children and adults with brain tumors. Practice is primarily outpatient with some 2,000 patient visits each year. A fully funded second year of laboratory research is available. Applicants for this position must be eligible for a California medical license and be board-eligible or board-certified in neurology, neurosurgery, or medical oncology. There are two positions available. Apply to: Michael Prados, MD, Department of Neurological Surgery, M-787, Neuro-Oncology Service, University of California, San Francisco, 505 Parnassus Avenue, San Francisco, CA 94143-0112. The University of California is an equal opportunity/affirmative action employer. Women and minorities are encouraged to apply.

Fellowships

Neurobehavior Fellowship

Emory University School of Medicine invites applications for a one- or two-year fellowship in behavioral neurology, beginning on or after July 1, 1992. The fellowship will offer exposure to the neurology and neuropsychology of dementia, stroke, head injury, temporal lobe epilepsy, movement disorders, and atypical psychiatric disorders.

The fellow will be encouraged to intensively participate in one of the research activities of the program. Current clinical research includes drug trials for Alzheimer's disease, cognitive evoked potentials in aging and stroke, and the behavioral problems associated with temporal lobe epilepsy. Current basic research involves cellular neuroanatomy and neurophysiology relating to neuronal injury.

Please send letter of inquiry and CV to:

Robert C. Green, MD
Neurobehavioral Program
EMORY UNIVERSITY
DEPARTMENT OF NEUROLOGY
Wesley Woods Center
1821 Clifton Road, NE
Atlanta, GA 30329
Telephone: (404) 728-6682

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NEUROEPIDEMIOLOGY: Training fellowship available for board-eligible neurologist beginning July 1, 1992, at the Sergievsky Center and Neurological Institute, Columbia-Presbyterian Medical Center. Opportunity to earn a MS or MPH in epidemiology at the School of Public Health and work on ongoing clinical studies. Special interest in cerebrovascular disease or epilepsy preferred. Address inquiries to: Dr. Ralph L. Sacco, Neurological Institute, 710 West 168th Street, New York, NY 10032. Columbia University is an equal opportunity employer.

FELLOWSHIP IN NEUROLOGY OF AGING — A fellowship is available for July, 1992, for the Neurobiology of Aging. The position includes opportunities for both clinical and basic research, as well as experience in the diagnosis and management of neurologic disorders occurring with age. The fellowship is for one or two years, and will include opportunities for participation in ongoing studies in neuropharmacology, neuropathology, molecular neurobiology, neuropsychology and the deisgn of clinical studies. Neurology residency training or equivalent experience is required. The fellowship is in the Neurology Department at the University of Massachusetts Medical Center. Reply to: David A. Drachman, MD, Professor and Chairman, Department of Neurology, University of Massachusetts Medical Center, 55 Lake Avenue North, Worcester, MA 01655 USA. EOE.

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INDICATIONS AND USAGE: Dilantin is indicated for the control of generalized tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.

Phenytoin serum level determinations may be necessary for optimal dosage adjustments (see Dosage and Administration and Clinical Pharmacology in the full prescribing information).

CONTRAINDICATIONS: Phenytoin is contraindicated in those patients who are hypersensitive to phenytoin or other hydantoins.

WARNINGS: Abrupt withdrawal of phenytoin in epileptic patients may precipitate status epilepticus. When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually. However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be necessary. In this case, alternative therapy should be an antiepileptic drug not belonging to the hydantoin chemical class.

There have been a number of reports suggesting a relationship between phenytoin and the development of lymphadenopathy (local or generalized) including benign lymph node hyperplasia, pseudolymphoma, lymphoma, and Hodgkin's Disease. Although a cause and effect relationship has not been established, the occurrence of lymphadenopathy indicates the need to differentiate such a condition from other types of lymph node pathology. Lymph node involvement may occur with or without symptoms and signs resembling serum sickness, eg, fever, rash and liver involvement.

In all cases of lymphadenopathy, follow-up observation for an extended period is indicated and every effort should be made to achieve seizure control using alternative antiepileptic drugs.

Acute alcoholic intake may increase phenytoin serum levels while chronic alcoholic use may decrease serum levels.

In view of isolated reports associating phenytoin with exacerbation of porphyria, caution should be exercised in using this medication in patients suffering from this disease.

Usage in Pregnancy: A number of reports suggests an association between the use of antiepileptic drugs by women with epilepsy and a higher incidence of birth defects in children born to these women. Data are more extensive with respect to phenytoin and phenobarbital, but these are also the most commonly prescribed antiepileptic drugs; less systematic or anecdotal reports suggest a possible similar association with the use of all known antiepileptic drugs.

The reports suggesting a higher incidence of birth defects in children of drug-treated epileptic women cannot be regarded as adequate to prove a definite cause and effect relationship. There are intrinsic methodological problems in obtaining adequate data on drug teratogenicity in humans; genetic factors or the epileptic condition itself may be more important than drug therapy in leading to birth defects. The great majority of mothers on antiepileptic medication deliver normal infants. It is important to note that antiepileptic drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and threat to life. In individual cases where the severity and frequency of the seizure disorder are such that the removal of medication does not pose a serious threat to the patient, discontinuation of the drug may be considered prior to and during pregnancy, although it cannot be said with any confidence that even minor seizures do not pose some hazard to the developing embryo or fetus. The prescribing physician will wish to weigh these considerations in treating or counseling epileptic women of childbearing potential.

In addition to the reports of increased incidence of congenital malformation, such as cleft lip/palate and heart malformations, in children of women receiving phenytoin and other antiepileptic drugs, there have more recently been reports of a fetal hydantoin syndrome. This consists of prenatal growth deficiency, microcephaly and mental deficiency in children born to mothers who have received phenytoin, barbiturates, alcohol, or trimethadione. However, these features are all interrelated and are frequently associated with intrauterine growth retardation from other causes.

There have been isolated reports of malignancies, including neuroblastoma, in children whose mothers received phenytoin during pregnancy.

An increase in seizure frequency during pregnancy occurs in a high proportion of patients, because of altered phenytoin absorption or metabolism. Periodic measurement of serum phenytoin levels is particularly valuable in the management of a pregnant epileptic patient as a guide to an appropriate adjustment of dosage. However, postpartum restoration of the original dosage will probably be indicated.

Neonatal coagulation defects have been reported within the first 24 hours in babies born to epileptic mothers receiving phenobarbital and/or phenytoin. Vitamin K has been shown to prevent or correct this defect and has been recommended to be given to the mother before delivery and to the neonate after birth.

PRECAUTIONS: General: The liver is the chief site of biotransformation of phenytoin; patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

A small percentage of individuals who have been treated with phenytoin has been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined.

Phenytoin should be discontinued if a skin rash appears (see "Warnings" section regarding drug discontinuation). If the rash is exfoliative, purpuric, or bullous or if lupus erythematosus, Stevens-Johnson syndrome, or toxic epidermal necrolysis is suspected, use of this drug should not be resumed and alternative therapy should be considered. (See Adverse Reactions.) If the rash is of a milder type (measles-like or scarlatiniform), therapy may be resumed after the rash has completely disappeared. If the rash recurs upon reinstitution of therapy, further phenytoin medication is contraindicated.

Phenytoin and other hydantoins are contraindicated in patients who have experienced phenytoin hypersensitivity. Additionally, caution should be exercised if using structurally similar (eg, barbiturates, succinimides, oxazolidinediones and other related compounds) in these same patients.

Hyperglycemia, resulting from the drug's inhibitory effects on insulin release, has been eported. Phenytoin may also raise the serum glucose level in diabetic patients.

Osteomalacia has been associated with phenytoin therapy and is considered to be due to henytoin's interference with Vitamin D metabolism.

Phenytoin is not indicated for seizures due to hypoglycemic or other metabolic causes. ppropriate diagnostic procedures should be performed as indicated.

Phenytoin is not effective for absence (petit mal) seizures. If tonic-clonic (grand mal) and bsence (petit mal) seizures are present, combined drug therapy is needed.

Serum levels of phenytoin sustained above the optimal range may produce confusional states referred to as "delirium," "psychosis," or "encephalopathy," or rarely irreversib
dysfunction. Accordingly, at the first sign of acute toxicity, plasma levels are recomm
reduction of phenytoin therapy is indicated if plasma levels are excessive; if symp
termination is recommended. (See Warnings.)

Information for Patients: Patients taking phenytoin should be advised of the ir
adhering strictly to the prescribed dosage regimen, and of informing the physician
condition in which it is not possible to take the drug orally as prescribed, eg, sur

Patients should also be cautioned on the use of other drugs or alcoholic beverage
seeking the physician's advice.

Patients should be instructed to call their physician if skin rash develops.

The importance of good dental hygiene should be stressed in order to r
development of gingival hyperplasia and its complications.

Do not use capsules which are discolored.

Laboratory Tests: Phenytoin serum level determinations may be necessary to ach
dosage adjustments.

Drug Interactions: There are many drugs which may increase or decrease pheny
which phenytoin may affect. Serum level determinations for phenytoin are espe
when possible drug interactions are suspected. The most commonly occurring drug
are listed below: 1. Drugs which may increase phenytoin serum levels include: a
intake, amiodarone, chloramphenicol, chlordiazepoxide, diazepam, dicumarol,
estrogens, H_2-antagonists, halothane, isoniazid, methylphenidate, phen
phenylbutazone, salicylates, succinimides, sulfonamides, tolbutamide, trazodon

2. Drugs which may decrease phenytoin levels include: carbamazepine, chronic al
reserpine, and sucralfate. Moban® brand of molindone hydrochloride contains c
which interfere with the absorption of phenytoin. Ingestion times of phenytoin
preparations containing calcium should be staggered in patients with low serum phe
to prevent absorption problems.

3. Drugs which may either increase or decrease phenytoin serum levels include: ph
sodium valproate, and valproic acid. Similarly, the effect of phenytoin on phenobarb
acid and sodium valproate serum levels is unpredictable.

4. Although not a true drug interaction, tricyclic antidepressants may precipitat
susceptible patients and phenytoin dosage may need to be adjusted.

5. Drugs whose efficacy is impaired b
include: corticosteroids, coumarin anti
digitoxin, doxycycline, estrogens, furos
contraceptives, quinidine, rifampin, th
vitamin D.

Drug/Laboratory Test Interactions: Phe
cause decreased serum levels of protein-b
(PBI). It may also produce lower than norm
dexamethasone or metyrapone tests. Phe
cause increased serum levels of glucose, al
phatase, and gamma glutamyl transpeptic

Carcinogenesis: See "Warnings" section f
tion on carcinogenesis.

Pregnancy: See Warnings.

Nursing Mothers: Infant breast-feeding is not recommended for women taking this dr
phenytoin appears to be secreted in low concentrations in human milk.

ADVERSE REACTIONS: Central Nervous System: The most common manifestations e
with phenytoin therapy are referable to this system and are usually dose-related. Th
nystagmus, ataxia, slurred speech, decreased coordination and mental confusion.
insomnia, transient nervousness, motor twitchings, and headaches have also been obse
have also been rare reports of phenytoin induced dyskinesias, including chorea, dysto
and asterixis, similar to those induced by phenothiazine and other neuroleptic drugs.

A predominantly sensory peripheral polyneuropathy has been observed in patient
long-term phenytoin therapy.

Gastrointestinal System: Nausea, vomiting, constipation, toxic hepatitis and liver

Integumentary System: Dermatological manifestations sometimes accompanied b
included scarlatiniform or morbilliform rashes. A morbilliform rash (measles-like) i
common; other types of dermatitis are seen more rarely. Other more serious forms
be fatal have included bullous, exfoliative or purpuric dermatitis, lupus erythematosu
Johnson syndrome, and toxic epidermal necrolysis (see Precautions).

Hemopoietic System: Hemopoietic complications, some fatal, have occasionally bee
in association with administration of phenytoin. These have included thrombocytope
penia, granulocytopenia, agranulocytosis, and pancytopenia with or without bone m
pression. While macrocytosis and megaloblastic anemia have occurred, these conditio
respond to folic acid therapy. Lymphadenopathy including benign lymph node hyperpl
dolymphoma, lymphoma, and Hodgkin's Disease have been reported (see Warning

Connective Tissue System: Coarsening of the facial features, enlargement of the lip
hyperplasia, hypertrichosis and Peyronie's Disease.

Cardiovascular: Periarteritis nodosa.

Immunologic: Hypersensitivity syndrome (which may include, but is not limited to,
such as arthralgias, eosinophilia, fever, liver dysfunction, lymphadenopathy or rash)
lupus erythematosus, immunoglobulin abnormalities.

OVERDOSAGE: The lethal dose in children is not known. The lethal dose in adults is
to be 2 to 5 grams. The initial symptoms are nystagmus, ataxia, and dysarthria. Othe
tremor, hyperreflexia, lethargy, slurred speech, nausea, vomiting. The patient ma
comatose and hypotensive. Death is due to respiratory and circulatory depression.

There are marked variations among individuals with respect to phenytoin plasma le
toxicity may occur. Nystagmus, on lateral gaze, usually appears at 20 mcg/mL, at
mcg/mL, dysarthria and lethargy appear when the plasma concentration is over 40 mc
as high a concentration as 50 mcg/mL has been reported without evidence of toxicity
as 25 times the therapeutic dose has been taken to result in a serum concentratio
mcg/mL with complete recovery.

Treatment: Treatment is nonspecific since there is no known antidote.

The adequacy of the respiratory and circulatory systems should be carefully obs
appropriate supportive measures employed. Hemodialysis can be considered since
is not completely bound to plasma proteins. Total exchange transfusion has been u
treatment of severe intoxication in children.

In acute overdosage the possibility of other CNS depressants, including alcohol,
borne in mind.

Caution – Federal law prohibits dispensing without prescription. 0

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As rare as a seizure on Dilantin® (extended phenytoin sodium capsules, USP) 100 mg

For as many as 86% of patients, seizures occur only once in a blue moon—if at all—once Dilantin monotherapy is under way.[1]

That fact holds true for partial, complex partial, generalized tonic-clonic seizures, and status epilepticus.

And it's achieved *without* significant cognitive impairment at therapeutic drug levels (10 to 20 μg/mL),[2] often *with* once-daily therapy (Dilantin® Kapseals®), which enhances compliance.

What you demand, Dilantin does—for millions of patients every day.

That's why Dilantin remains a drug of choice.

And that's why most patients on Dilantin will wait a long, long time to see another seizure.

Dilantin®

Once in a blue moon" describes the phenomenon in which the moon appears as a brilliant blue. Seen worldwide following the volcanic eruption of Krakatoa in 1883, the blue moon occurs only when atmospheric cloud droplets, each less than 5 μm in diameter, form in abundance—an exceedingly rare event.[3]

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References

1. Ramsay RE, Wilder BJ, Berger JR, et al: A double-blind study comparing carbamazepine with phenytoin as initial seizure therapy in adults. *Neurology* 1983;33:904-910.
2. Porter RJ, Theodore WH: Nonsedative regimens in the treatment of epilepsy. *Arch Intern Med* 1983;143:945-947.
3. Shute CCD: The 'blue moon' phenomenon. *Weather* 1976; 31:292-296.

Please see adjacent page for brief summary of prescribing information.

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